Recent Advances in Tandem Reductive Processes

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Recent Advances in Tandem Reductive Processes

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Abstract

The research presented herein is concerned with the exploration of tandem processes initiated by the conjugate reduction of Michael acceptors, encompassing the asymmetric reductive Dieckmann reaction and the two-carbon homologation of aldehydes by two complementary methodologies.

Chapter 1 introduces the area of transition metal catalysed tandem reductive processes as a tool for carbon-carbon bond formation. An extensive discussion of this methodology is included and recent advances in the area are highlighted.

Chapter 2 discusses the initial study into the asymmetric reductive Dieckmann condensation. 3,3'-Disubstituted 4-oxopyrrolidines were synthesised in up to 93% ee using both molybdenum and copper catalysis.

Chapter 3 describes the novel molybdenum-catalysed two-carbon homologation of aldehydes by the reduction of alkylidene Meldrum's acid derivatives. No over reduction to the corresponding alcohol is observed, as the aldehyde functionality remains protected until hydrolysis.

Chapter 4 discusses the mild, expeditious amine promoted reduction of cyclic malonates to β-substituted propionaldehydes. The synthetic utility of the methodology is demonstrated by the synthesis of *γ*-substituted propylamines in a one-pot hydrosilylation/reductive amination process.

Chapter 5 describes the synthesis and characterisation for the compounds discussed in chapters 2, 3 and 4.

Acknowledgments

I would like to thank Dr. Chris Frost for the support and guidance he has offered me over the past three years. It has been a great pleasure working for you.

I would also like to thank all the members of the Frost group past and present, especially Joe Allen, Jimmy White, Hannah Edwards, Jon Sharp, Dr Jon Hargrave, Dr Steve Penrose, Dr. Chris Chapman, Dr. Jerome Le Notre, Dr. Ludivine Zoute and Dr. Steve Flower. I have really appreciated all the support, academic or otherwise, you all have offered me. Thanks also to Simon Pridmore, Steve Reade, Tom Douglas and Olly Saker, we have, just about, kept ourselves sane.

I must also thank all the musicians, footballers and those who went to Philadelphia and Barcelona for such memorable times.

Finally, I'd like to thank Halima for her unbelievable patience, support and encouragement; and also my parents and brothers for their constant support.

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List of Abbreviations

Ac	acetyl
acac	acetylacetonate
Anal.	analytical (spectrometry)
app.	apparent
aq	aqueous
Ar	aryl
Bn	benzyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINAPO	2,2'-bis(diphenylphosphine oxide)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
BIPHEP	2,2'-bis(diphenylphosphino)-1,1'-biphenyl
Boc	*tert*-butylcarbonyl
br	broad (spectral)
Bu	normal (primary) butyl
^{t}Bu	*tert*-butyl
^{o}C	degrees Celsius
calcd	calculated
cat.	catalytic quantity
Cbz	carboxybenzyl
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
coe	cyclooctene
δ	chemical shift in parts per million downfield from tetramethylsilane
COSY	correlation spectroscopy
cy	cyclohexyl
d	doublet (spectral)
DBU	1,8-diazobicyclo[5.4.0]undecane
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
dcpe	1,1'-bis(dicyclohexylphosphino)ethane
DCU	*N*,*N*'-dicyclohexylurea
^{o}	degrees (angle)
DIBAL	diisobutylaluminium hydride
DIFLUO-PHOS	5,5'-bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole
DMAP	4-(*N*,*N*'-dimethylamino)pyridine
DMF	dimethylformamide
DME	dimethoxyethane
DMSO	dimethyl sulfoxide
DOLEFIN	5-benzyl-8-methoxy-1,8-dimethyl-2-(2'-methylpropyl)bicyclo[2.2.2]octa-2,5-diene
dpm	dipivoylmethane
dppb	1,2'-bis(diphenylphosphino)butane
dppe	1,4'-bis(diphenylphosphino)ethane

dppf	1,1'-bis(diphenylphosphino)ferrocene
dppm	bis(diphenylphosphino)methane
DTBM	3,5-di-*tert*-butyl-4-methoxyphenyl
DuPhos	1,2-bis((2*R*,5*R*)-2,5-dimethylphospholano)benzene
ee	enantiomeric excess
EI	electron impact
ESI	electospray ionisation
Et	ethyl
equiv	equivalent(s)
fur	furyl
g	gram(s)
h	hour(s)
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared
J	coupling constant (in NMR spectroscopy)
JOSIPHOS	1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine
L	litre(s)
LDA	lithium diisopropylamide
lit.	literature
μ	micro
m	milli; multiplet (spectral)
M	molar (moles per litre)
M^+	parent molecular ion
MA	Meldrum's acid
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
MVK	methyl vinyl ketone
MW	microwave
m/*z*	mass-to-charge ratio (in mass spectrometry)
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Ns	*p*-nitrobenzenesulfonyl
PCC	pyridinium chlorochromate
Ph	phenyl
Phanephos	4,12-bis(diphenylphosphino)-[2.2]-paracyclophane
Phebox	bisoxazolinylphenyl
PMHS	polymethylhydrosiloxane
P-Phos	2,2′,6,6′-tetramethoxy-4,4′-bis(diphenylphosphino)-3,3′-bipyridine
ppm	part(s) per million

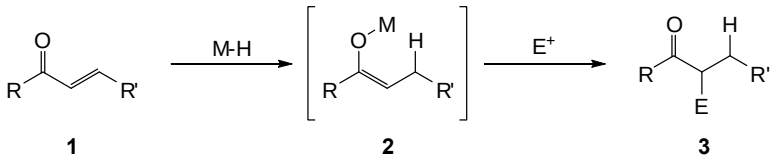
Pr	propyl
^{i}Pr	*iso*-propyl
Py	pyridine
q	quartet (spectroscopic)
quin	quintet (spectroscopic)
rac	racemic, racemate
R_f	retention factor (in chromatography)
r.t.	room temperature
s	singlet (spectral)
SEGPHOS	5,5′-bis[diphenylphosphino]-4,4′-bi-1,3-benzodioxole
sept	septet (spectral)
SYNPHOS	5,5′-bis[diphenylphosphino]-4,4′-bi-1,4-benzodioxine
t	triplet (spectral)
TANIA-PHOS	1-dicyclohexylphosphino-2-[(*S*)-α-(dimethylamino)-2-(dicyclohexylphosphino)benzyl]ferrocene
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBS	tributylsilyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMDS	tetramethyldisiloxane
TMS	trimethylsilyl; tetramethylsilane
tol	toluene
t_R	retention time (in chromatography)
Ts	*p*-toluenesulfonyl

Chapter 1 - Tandem Catalytic Reductive Processes

1.1 Introduction

The formation of new carbon-carbon bonds is one of the most important challenges within organic synthesis. Of the numerous methods of carbon-carbon bond formation available to the modern synthetic organic chemist, those involving the nucleophilic attack of silyl enol ethers or silyl ketene acetals on electrophilic carbon centres has proved to be of great importance, especially the Mukaiyama aldol reaction.[1] The 2009 review by Kalesse *et al*. on the use of highly stereoselective aldol reactions in the total synthesis of natural products highlights the recent progress and applications of the aldol reaction.[2]

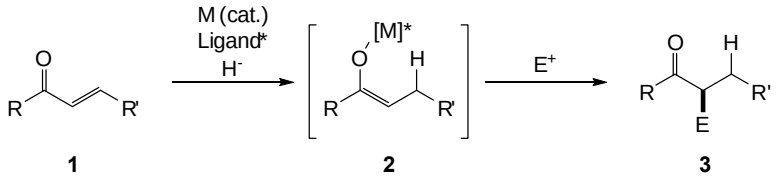
Despite being a methodological cornerstone of organic synthesis, enolate chemistry has its limitations. For example, formation of the desired enolate requires either a completely separate synthetic step or the chemo- and regioselective deprotonation of pro-nucleophiles. A particularly attractive method of efficient *in situ* generation of enolates is the use of enones as "latent enolates".[3] The use of enones as latent enolates enables regioselective enolate formation from relatively robust precursors. These enolates can then react with the desired electrophilic partner (Scheme 1).



Scheme 1 Tandem processes initiated by the conjugate reduction of enones

Development of catalytic variations of this tandem methodology has greatly focused on the formation of enolates from enones by hydrometallation and has been addressed in a number of reviews.[3-7] Efficient and highly selective processes have been developed using transition metal salt precatalysts, chiral ligands and stoichiometric reductants. A range of different stoichiometric reductants has been used such as silanes, molecular hydrogen, stannanes and

boranes. The use of chiral ligands results in the formation of chiral metal enolates which allow for the stereoselective nucleophilic attack of the enolate on the carbon electrophile resulting in the formation of new stereogenic centres (Scheme 2).



Scheme 2 Enantioselective tandem reductive processes

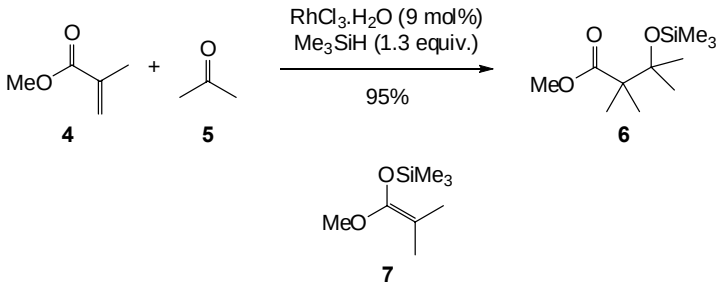
This review will map the recent progress made in tandem reductive processes focusing on those processes initiated by the hydrometallation and hydrosilylation of Michael acceptors.

1.2 Reductive Aldol Reactions

1.2.1 Rhodium-Catalysed Reductive Aldol Reactions

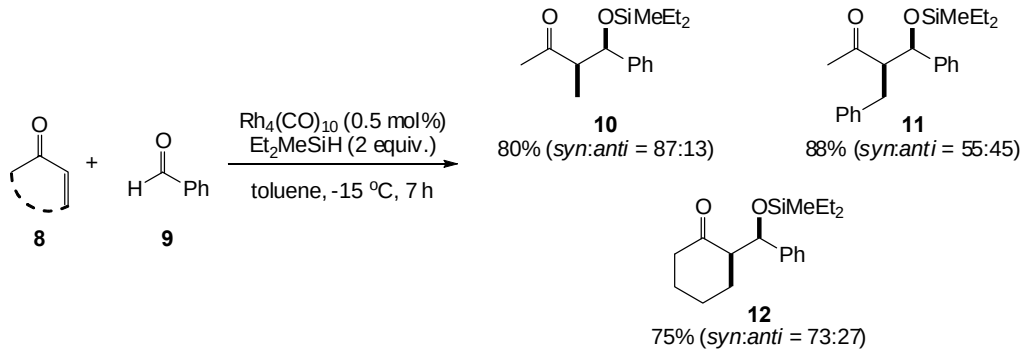
1.2.1.1 Initial Studies

Revis and Hilty reported the first reductive aldol reaction.[8] Catalysed by rhodium chloride, methyl methacrylate **4** was coupled with excess acetone **5** using trimethylsilane as a hydride source giving the β-siloxy ester **6** in a 95% yield (Scheme 3). No aldol product was observed on reacting silyl ketene acetal **7** (synthesised independently) with acetone in the presence of rhodium chloride, suggesting the reaction proceeded *via* a rhodium ketene acetal (Scheme 3).

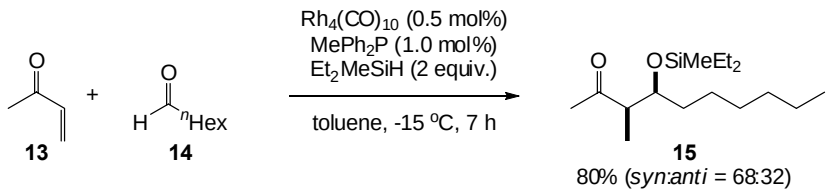


Scheme 3 The first example of a reductive aldol reaction

Matsuda *et al*. formed β-siloxy ketone aldols by the reductive coupling of α,β-unsaturated ketones with aldehydes in the presence of $Rh_4(CO)_{12}$ and Et_2MeSiH; *syn*-selectivity was observed for this transformation (Scheme 4).[9] It was also found that the addition of $MePh_2P$ enabled the reductive coupling of enolisable aldehydes such as hexanal (Scheme 5).



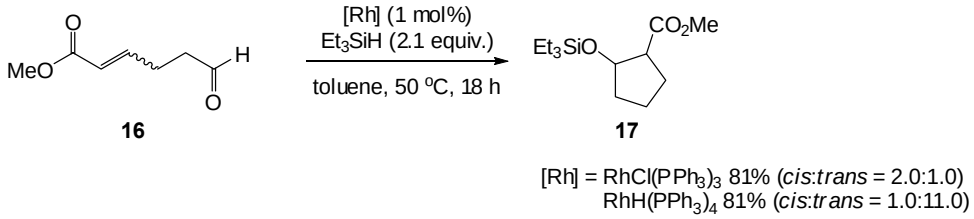
Scheme 4 Rhodium-catalysed reductive aldol reaction between enones and benzaldehyde



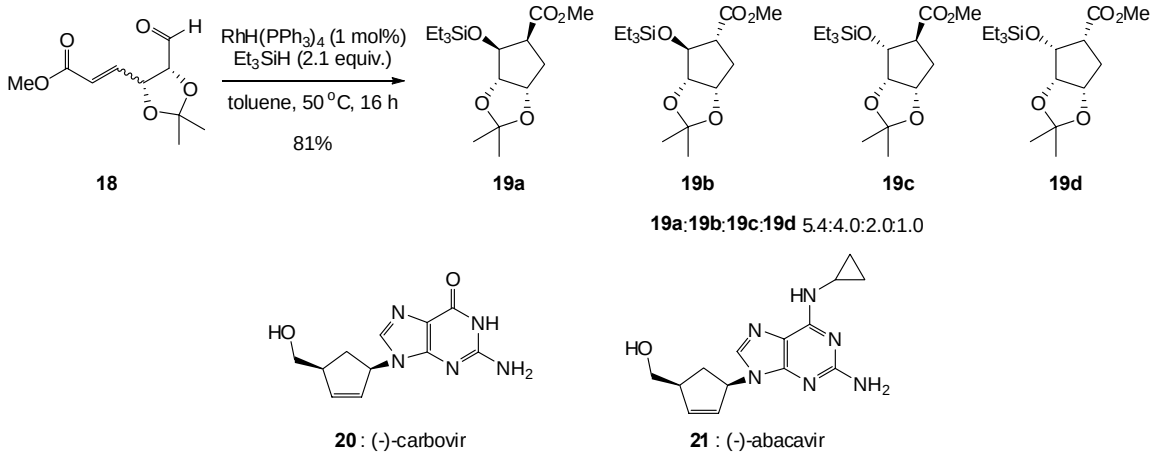
Scheme 5 Rhodium-catalysed reductive aldol reaction between methyl vinyl ketone and hexanal

Motherwell and Whitehead reported the rhodium-catalysed intramolecular reductive aldol reaction, it was found that by simply changing the catalyst precursor a switch between *cis*- and *trans*-selectivity could be achieved.[10,11] On using $RhCl(PPh_3)_3$ *cis*-selectivity was observed and using $RhH(PPh_3)_4$ *trans*-selectivity was achieved (Scheme 6). Five-, six- and seven-membered ring products were accessed with substitution on the carbon backbone

being tolerated. This method also allowed for the synthesis of bicyclic systems. It was also observed that the selectivity of the catalytic precursors was a general, not absolute, trend.[11] Motherwell and Whitehead applied this methodology to the formal enantioselective synthesis of (–)-carbovir **20** and (–)-abacavir **21**.[12] Exposure of protected diol containing 6-oxohexanoate **18** to the reductive conditions gave a separable mixture of diastereomers, which, through further manipulations, led to the synthesis of these biologically active targets (Scheme 7).



Scheme 6 Rhodium-catalysed intramolecular reductive aldol reaction

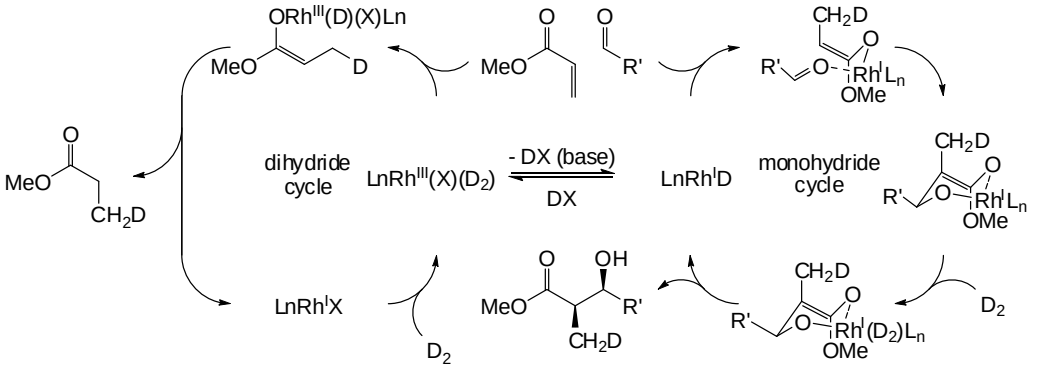


Scheme 7 Key synthetic step towards the synthesis of (-)-carbovir and (-)-abacavir

1.2.1.2 Hydrogen Mediated Processes

Often, transition metal catalysed reduction of Michael acceptors are mediated by a stoichiometric hydride source, such as a silane. The use of molecular hydrogen offers a convenient, atom-economic solution to the use of a stoichiometric reductant, bypassing the removal of undesirable byproducts from the reaction mixture.[13,14]

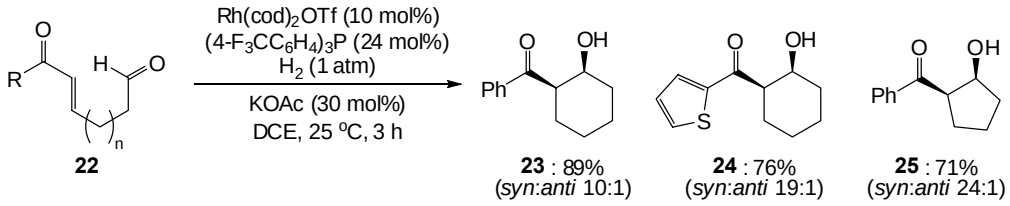
Krische has pioneered the reductive aldol reaction mediated by molecular hydrogen, with both *syn*-selective inter- and intramolecular transformations being carried out.[5,15] Competitive alkene hydrogenation of the Michael acceptor was suppressed by the use of a cationic rhodium precatalyst and an inorganic base (typically KOAc or Li_2CO_3).[16] Mechanistic studies revealed the base converts the rhodium(III)-dihydride species, responsible for alkene hydrogenation *via* the dihydride cycle (Scheme 8), into the desired rhodium(I)-monohydride species which catalyses the reductive aldol process *via* the monohydride cycle (Scheme 8).[5]



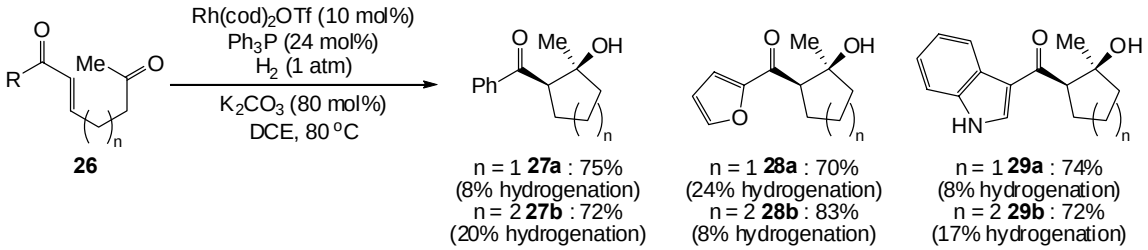
Scheme 8 Competitive alkene hydrogenation and reductive aldol reactions

Early research focused on the intramolecular reductive aldol cyclisation of aldo-enones[16] and keto-enones[17,18] with five- and six-membered rings being formed in high yields and with excellent *syn*-selectivity (*syn*:*anti* >95:5 for all keto-enones). Reactions involving aldo-enones under optimised conditions show trace amounts of alkene hydrogenation product (Scheme 9). However, on moving to keto-enones, increased amounts of alkene hydrogenation occurs due to the decreased electrophilicity of the ketone (Scheme 10).[17] The efficient reductive aldol cyclisation of keto-enones was achieved using the more

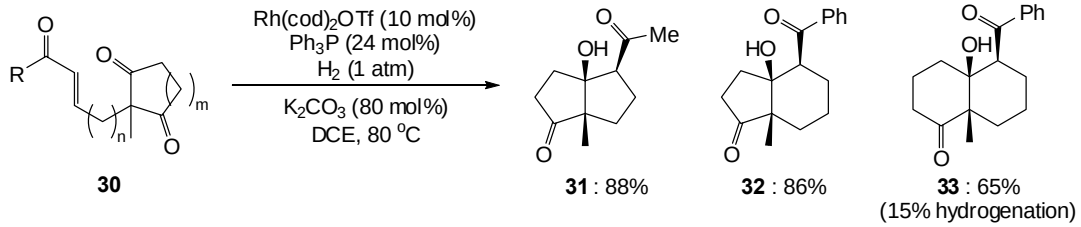
electrophilic 1,3-diones **30** (Scheme 11); no conjugate reduction product was observed for these keto-enones except in the formation of the strained *cis*-decalone **33**.[18]



Scheme 9 Reductive aldol cyclisation of aldo-enones under hydrogenation conditions

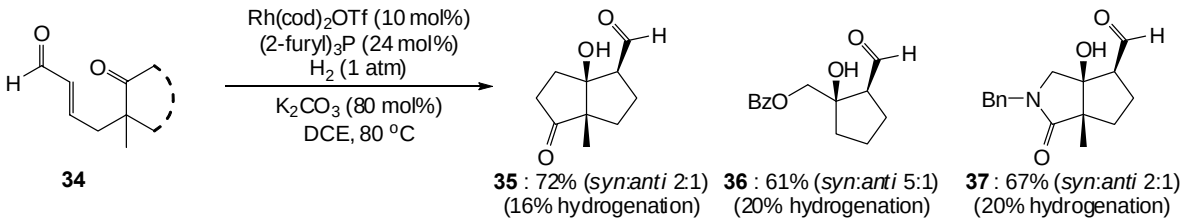


Scheme 10 Reductive aldol cyclisation of keto-enones *via* catalytic hydrogenation



Scheme 11 Reductive aldol cyclisation of enone-diones *via* catalytic hydrogenation

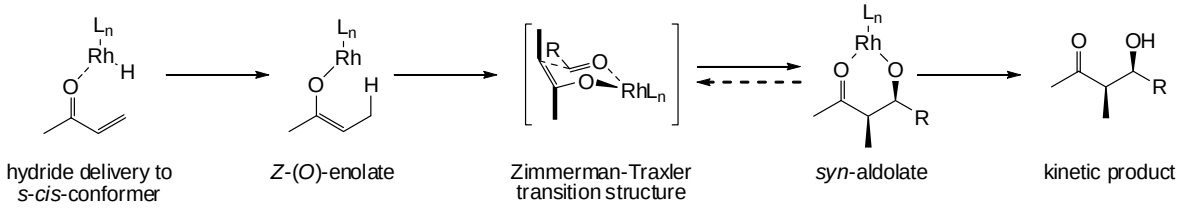
Krische *et al*. also described the challenging intramolecular reductive aldol reaction of enal-ketones (Scheme 12).[18] Low yields were observed with triphenylphosphine, however, π-acidic ligand tri(2-furyl)phosphine increased yields. Poor to moderate *syn*-selectivity was observed along with varying quantities of undesirable conjugate reduction product.



Scheme 12 Reductive aldol cyclisation of enal-ketones *via* catalytic hydrogenation

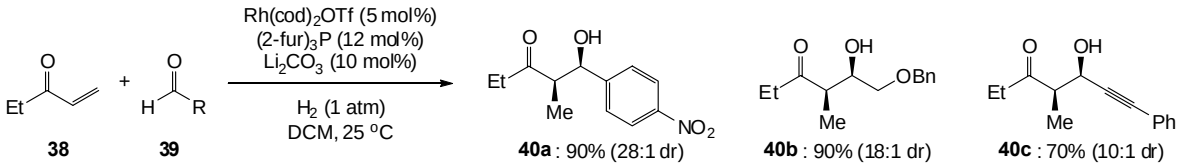
The intermolecular reductive aldol couplings of vinyl ketones with aryl aldehydes was investigated in Krische's original paper, however, only poor *syn*-selectivity was observed (typically *syn*:*anti* 2:1).[16] Further investigation showed that excellent *syn*-selectivity could be achieved when using the π-acid phosphine ligand tri(2-furyl)phosphine and Li_2CO_3.[19]

Hydrometallation is thought to result in a *Z*-(*O*)-enolate which undergoes aldolisation *via* a Zimmerman-Traxler-type transition structure (Scheme 13). The addition of tri(2-furyl)phosphine increases the Lewis acidity of the rhodium centre, therefore promoting the formation of the kinetically favourable *syn*-diastereomer by the tightening of the chair like transition state and favouring the kinetic pathway by mitigating retro-aldol cyclisation.

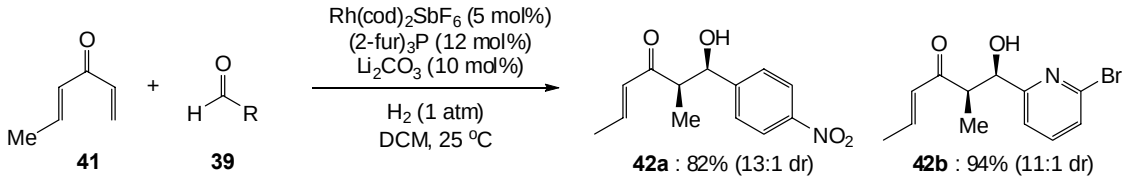


Scheme 13 Postulated route to *syn*-aldol product

Under these conditions, it was found that reduction of normally hydrogen-labile functionalities did not occur; alkynes, alkenes, benzylic ethers and nitroarenes remained intact (Scheme 14).[19] This reductive coupling was extended from methyl- and ethyl vinyl ketone to the divinyl ketone **41** with chemoselective reduction occurring only at the less substituted alkene; no further reduction of the aldol product was observed (Scheme 15).[20]

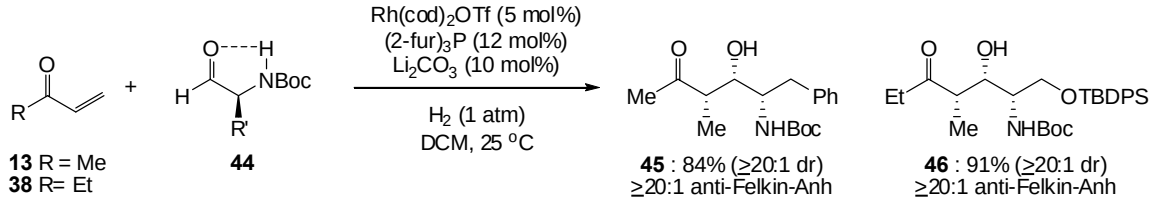


Scheme 14 Reductive coupling of vinyl ketones and aldehydes containing hydrogen-labile groups



Scheme 15 Regioselective reductive aldol reaction between aldehydes and divinyl ketones

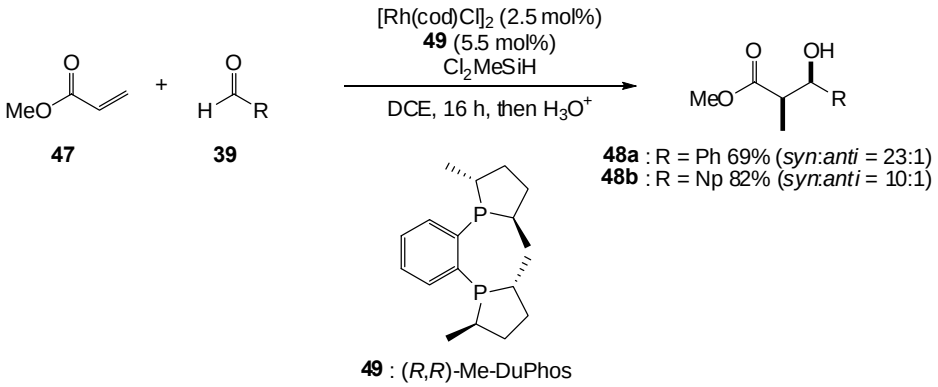
These neutral conditions also allow for the reductive aldol reaction between α,β-unsaturated ketones and chiral *N*-Boc-α-amino aldehydes without any deprotection of the amine functionality or racemisation of the chiral centre (Scheme 16).[21] In this study Krische *et al*. attribute the excellent levels of *syn*-aldol diastereoselectivity and anti-Felkin-Ahn control to the intramolecular hydrogen bonding in the amino aldehyde.



Scheme 16 *syn*-Diastereoselective hydrogenative aldol coupling between vinyl ketones and α-amino aldehydes

1.2.1.3 Asymmetric Rhodium-Catalysed Reductive Aldol Reactions

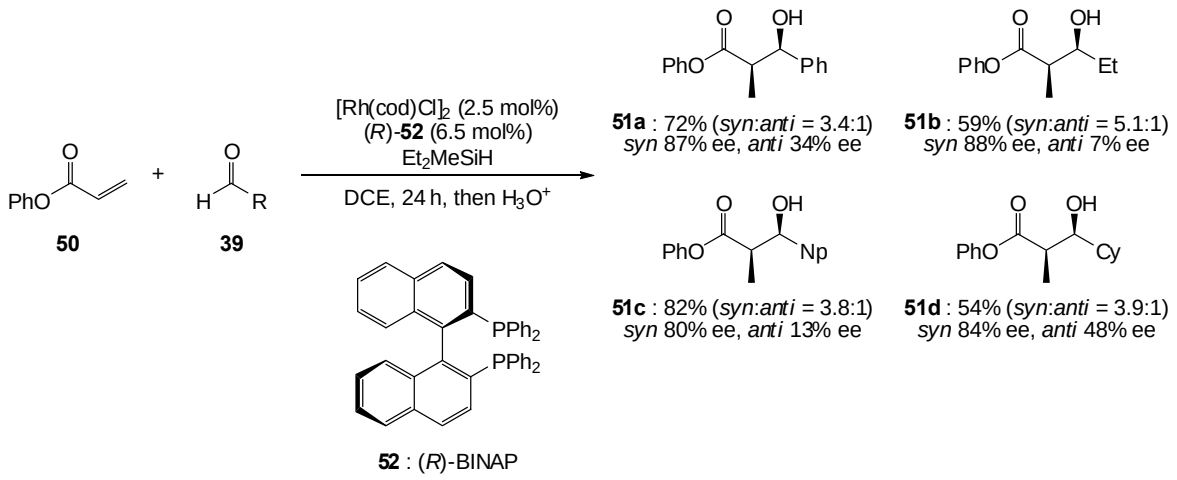
Morken *et al*., in 1999, carried out a catalyst evaluation, screening metal precatalysts, hydride sources and phosphine ligands in an array format.[22] The study revealed that $[Rh(cod)Cl]_2$, (*R*,*R*)-Me-DuPhos **49** and Cl_2MeSiH gave the desired product in both high yields, up to 82% isolated yield, and diastereoselectivity, up to *syn*:*anti* 23:1 (Scheme 17).



Scheme 17 Rhodium-catalysed reductive aldol reaction ligated by bisphosphine

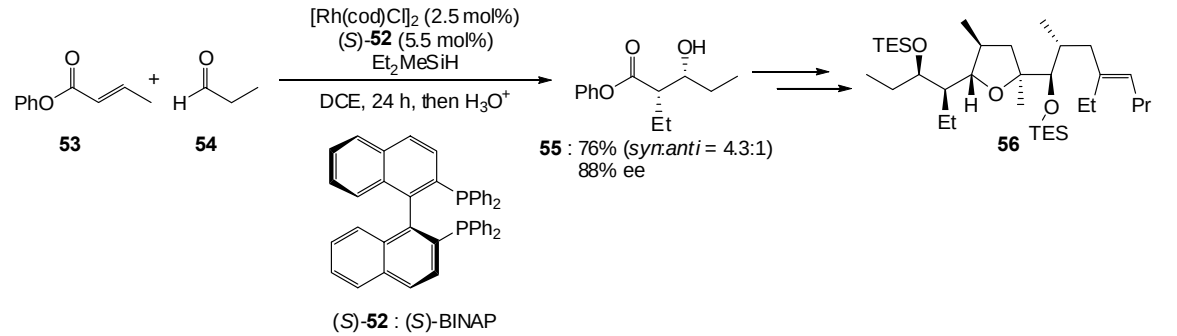
Further studies by Morken *et al*. into the reductive conditions described above showed that excellent diastereoselectivities of >60:1 (*syn*:*anti*) could be achieved in a two step process in which the required aldehyde was added to the reaction mixture after rhodium-catalysed hydrosilylation had occurred.[23]

In both Morken's one- and two-step rhodium-catalysed reductive aldol reactions it is the silyl ketene acetal, formed after hydrosilylation of the Michael acceptor, which is involved in the carbon-carbon bond forming process. Therefore, the chiral rhodium – bisphosphine species is not involved in the key step in which chirality is installed. However, using Et_2MeSiH as the stoichiometric reductant and (*R*)-BINAP as the bisphosphine ligand Morken *et al*. carried out asymmetric rhodium-catalysed reductive aldol reactions.[24] While *syn*:*anti* selectivities and yields in this study were moderate, good enantioselectivities were observed for the major *syn*-diastereomer (Scheme 18). This asymmetric transformation was carried out during the initial arrayed catalyst evaluation, however, a poor yield (4% yield) and enantioselectivity (20% ee) was observed. This was attributed to incomplete complexation during the microscale reaction.



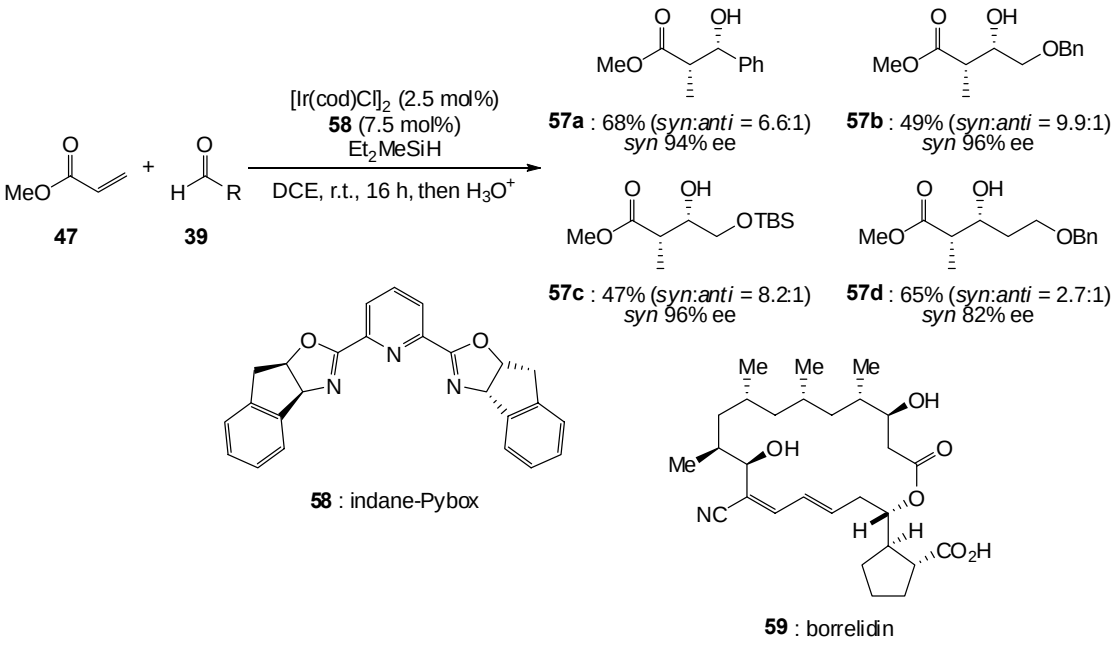
Scheme 18 Asymmetric rhodium-catalysed reductive aldol reaction

Although further studies by Morken *et al*. into this reactivity of the asymmetric rhodium-catalysed reductive aldol reaction resulted in little improvement in terms of yield and selectivity, greater mechanistic insight was achieved.[25] The dinuclear μ-hydride bridged Rh(I) species, [(BINAP)Rh-H/H-Rh(BINAP)] was postulated to be the active hydride species generated *in situ* from (*R*-BINAP)Rh(COD)BF_4 and $PhMe_2SiH$. Morken *et al*. also showed that without acidic hydrolysis the silyl protected aldol product could be isolated.[26] Reductive aldol product **55** was found to be a precursor to the C_{10}-C_{24} ketone fragment of the inostamycin family of polyether antibiotics **56** (Scheme 19); synthesis of this fragment also uses a reductive Claisen rearrangement which will be discussed later (*cf*. 1.8).[27]



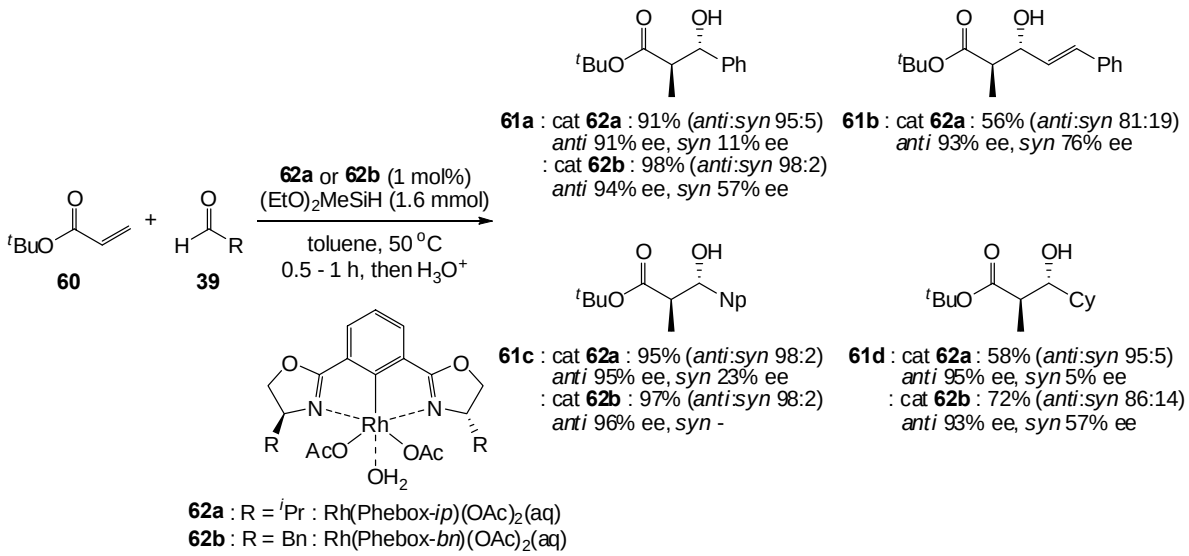
Scheme 19 A key step in the synthesis of the C_{10}-C_{24} ketone fragment of inostamycins

Remaining with the group 9 transition metals, Morken *et al*. used indane-Pybox **58** in the asymmetric iridium-catalysed reductive aldol reaction (Scheme 20). This showed greater enantio- and diastereocontrol than the previously reported rhodium – BINAP system, however, reaction scope was limited to benzaldehyde and α-alkoxy aldehydes.[28] The aldol product **57b** was used by Morken *et al*. as a precursor in the synthesis of biologically active macrocyclic borrelidin **59**.[29]



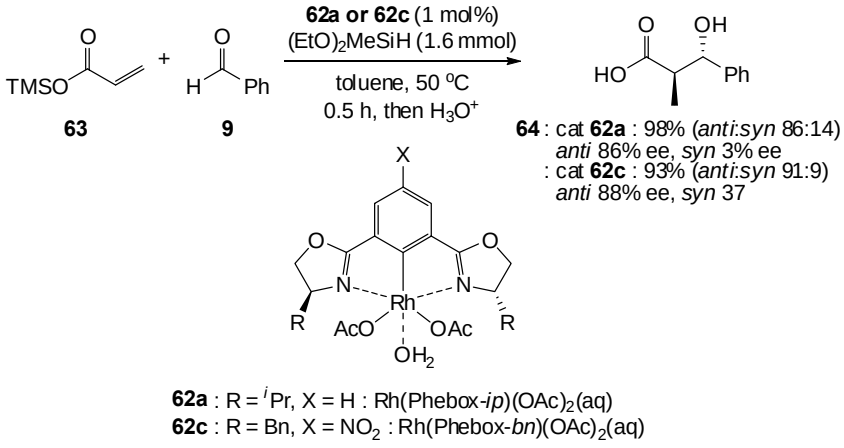
Scheme 20 Asymmetric iridium-catalysed reductive aldol reaction

Both Morken's rhodium- and iridium-catalysed reductive aldol processes are moderately *syn*-diastereoselective. Nishiyama *et al*. developed conditions, formerly used for conjugate reduction,[30,31] to allow for a highly *anti*-selective rhodium-catalysed reductive aldol reaction to proceed using Rh(Phebox) catalysts **62a** and **62b** along with a range of alkoxy- and alkylsilanes.[32] With very short reaction times (0.5 – 1 hour), a number of different aldehydes were coupled with *tert*-butyl acrylate (Scheme 21). Aromatic aldehydes gave consistently high *anti*-selectivities (up to 98:2) and enantioselectivities (up to 96% ee), while cinnamaldehydes and aliphatic aldehydes proved to be more challenging.



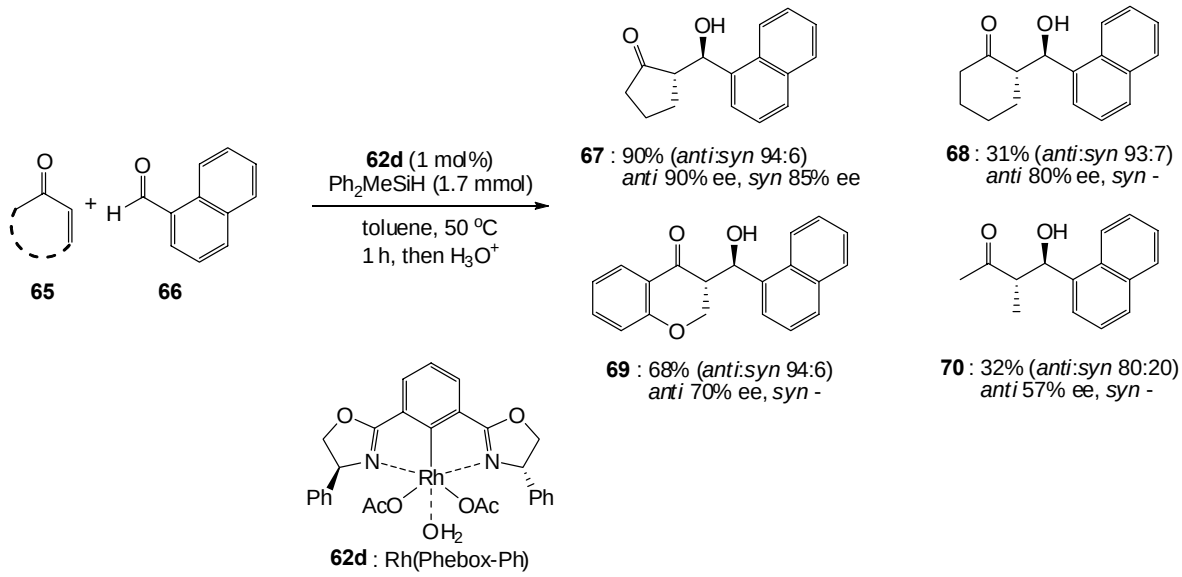
Scheme 21 Highly *anti*-selective rhodium-catalysed reductive aldol reaction

Although further modifications of the Phebox skeleton resulted in a detrimental effect on the *anti*-selectivity of the process, it did allow for the synthesis of β-hydroxy carboxylic acids by the hydrolysis of the reductive aldol product (Scheme 22).[33,34]



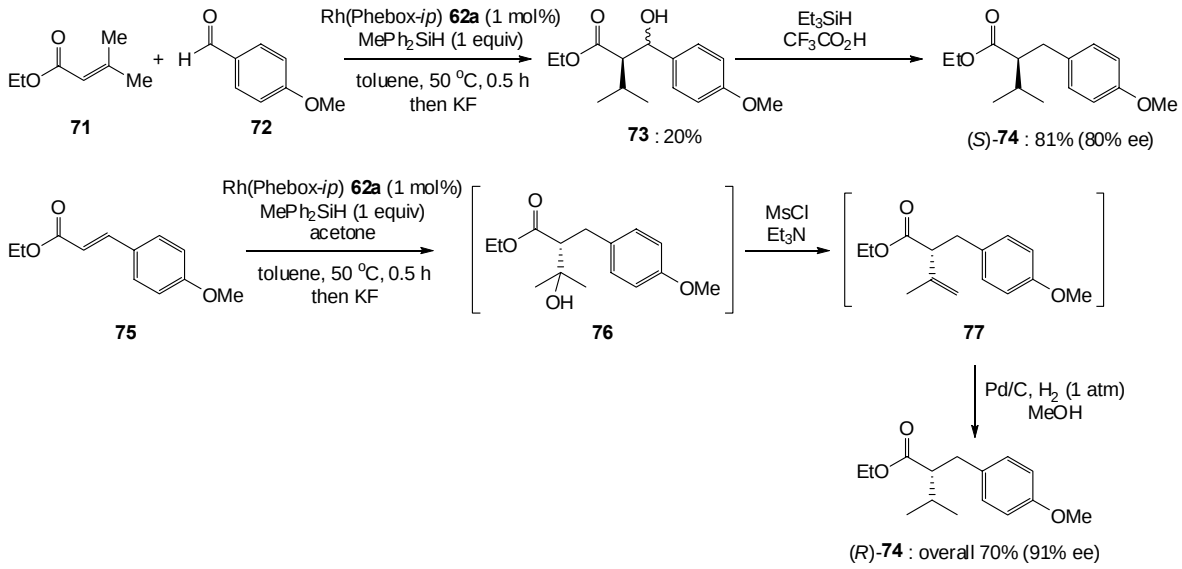
Scheme 22 Asymmetric synthesis of β-hydroxy carboxylic acids

Using Rh(Phebox-Ph) **62d**, Nishiyama *et al*. were able to couple cyclopentenone and aryl aldehydes with excellent *anti*-selectivity as well as high yields and enantioselectivities for the favoured *anti*-product. However, yields and selectivities for this transformation tail away on using other cyclic enones and vinyl methyl ketone (Scheme 23).[35]



Scheme 23 Intermolecular reductive coupling of enones and aldehdyes

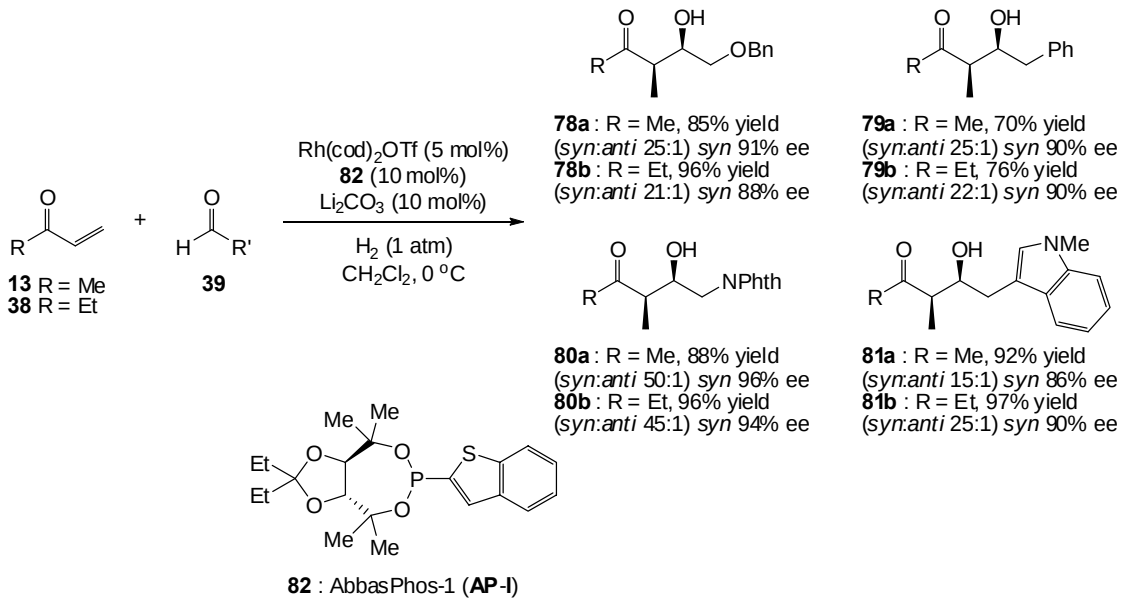
Nishiyama *et al*. also observed high yields and selectivities when applying their Rh(Phebox) reductive system to the reductive coupling of acrylates and ketones.[36] The reductive coupling of acrylates with both aldehydes and ketones enabled Nishiyama *et al*. to access both enantiomers of the α-chiral dihydroxinnamate **74** using the same chiral ligand.[37] Reductive coupling of **71** with *p*-anisaldehyde **72** and subsequent dehydroxyation gave (*S*)-**74**, while reductive coupling of **75** with acetone and subsequent dehydration and reduction gave (*R*)-**74** (Scheme 24).



Scheme 24 Synthesis of α-chiral dihydrocinnamates

Krische *et al*. were faced with a number of challenges on attempting asymmetric hydrogenative aldol couplings mediated by molecular hydrogen.[38] Firstly, only trace amounts of product were observed when a chelating phosphine ligand was used. Secondly, as seen in prior studies,[18-21] π-acidic ligands were required. Finally, commercially available chiral π-acidic phosphine ligands, such as phosphites and phosphoramidites derived from BINOL, gave only trace quantities of product; these ligands were considered too π-acidic.

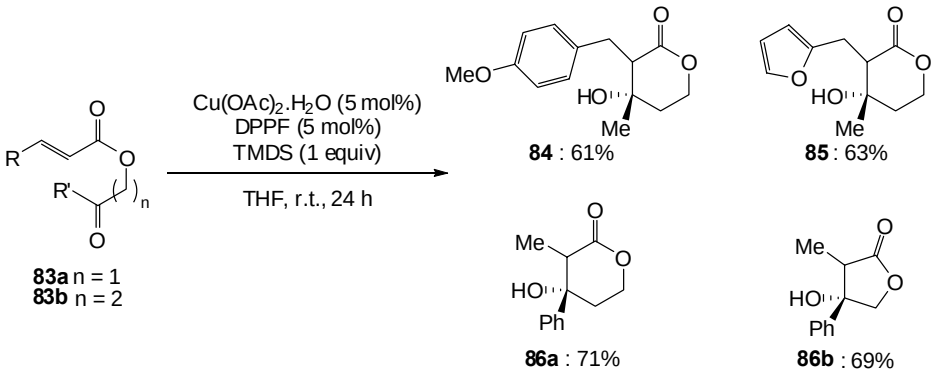
By ligand design and structural optimisation, Krische *et al*. identified TADDOL-based phosphonite **82** to be an effective monodentate ligand for the enantioselective hydrogenative aldol coupling of vinyl ketones with aldehydes (Scheme 25).[38] High yields (70-97%) and excellent enantioselectivities (86-96%) were observed for reductive coupling of vinyl ketones and α- and β-heteroatom substituted aldehydes as well as α-(hetero)aryl substituted aldehydes. When using acrylates only conventional hydrogenation was observed. It was also found that less activated aldehydes could not be tolerated in this reaction.



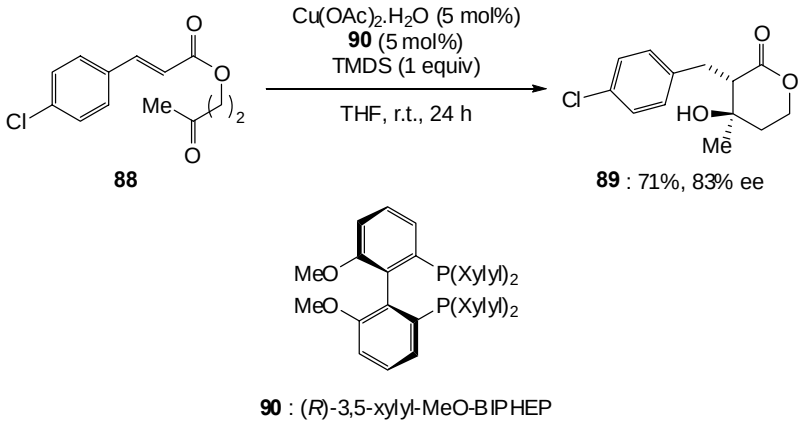
Scheme 25 Asymmetric rhodium-catalysed reductive aldol reaction mediated by molecular hydrogen

1.2.2 Copper-Catalysed Reductive Aldol Reactions

Following a number of studies into the copper-catalysed reductive aldol reaction using the phosphine stabilized hexamer Stryker's reagent, $[Ph_3PCuH]_6$,[39-45] and encouraged by the development of the asymmetric copper-catalysed conjugate reduction reaction,[6,46] Lam *et al*. reported the diastereo- and enantioselective synthesis of β-hydroxylactones.[47] Lam found $Cu(OAc)_2.H_2O$ to be a convenient copper salt for the transformation along with the inexpensive siloxane 1,1,3,3-tetramethylhydrosiloxane (TMDS) and either DPPF or *rac*-BINAP. Moderate yields of diastereotopically pure β-hydroxylactones were observed for both five- and six-membered rings, despite the former's 5-(enolendo)-*exo-trig* cyclisation being formally disfavoured by Baldwin's rules (Scheme 26).[48] A range of chiral bisphosphines was screened and enantioselectivities of up to 83% ee were observed when (*R*)-3,5-xylyl-MeO-BIPHEP **90** was employed as the ligand (Scheme 27).

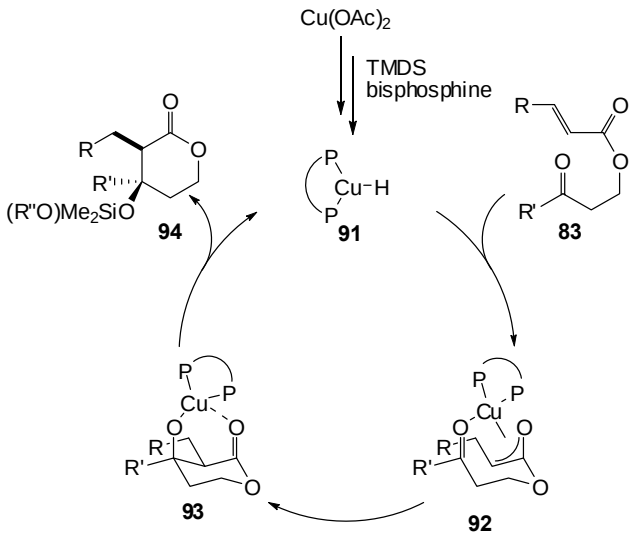


Scheme 26 Copper-catalysed synthesis of β-hydroxylactones



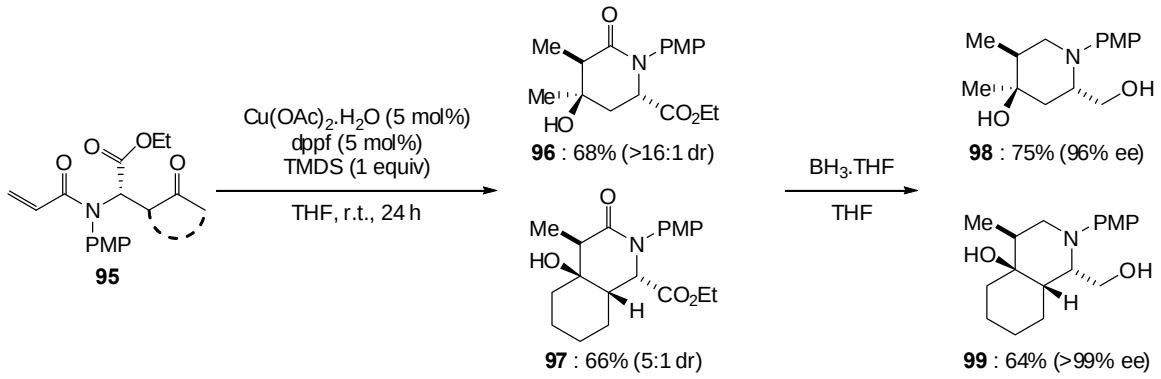
Scheme 27 Asymmetric copper-catalysed β-hydroxylactone synthesis

Lam proposed a catalytic cycle initiated by the formation of a copper-(I)-bisphosphine hydride complex **91** from $Cu(OAc)_2$, TMDS and a bisphosphine ligand. Hydrometallation of substrate **83** forms the copper enolate **92**, carbon-carbon bond formation then occurs to give aldolate **93**. Reaction of **93** with TMDS gives copper-(I)-complex **91** and silylated product **94** which undergoes protodesilylation on acidic work-up (Scheme 28).



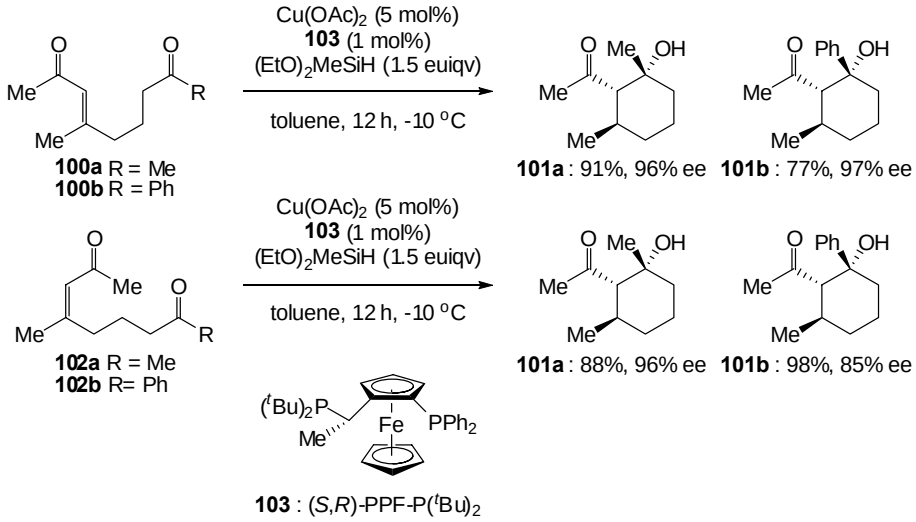
Scheme 28 Proposed mechanism for the copper-catalysed reductive aldol reaction

By moving from an intramolecular reductive aldol reaction using keto-acrylates to those using keto-acrylamides, Lam *et al*. synthesised 4-hydroxypiperidin-2-ones.[49] Yields of 4-hydroxpiperidin-2-ones were comparable to those observed for the synthesis of β-hydroxylacones (Scheme 29). The enantioselective synthesis of highly functionalised piperidin-2-ones from enantiomerically enriched substrates was achieved using this methodology; reduction of piperidin-2-ones **96** and **94** gave the potentially biologically active polyhydroxylated piperidines **98** and **99** (Scheme 29).



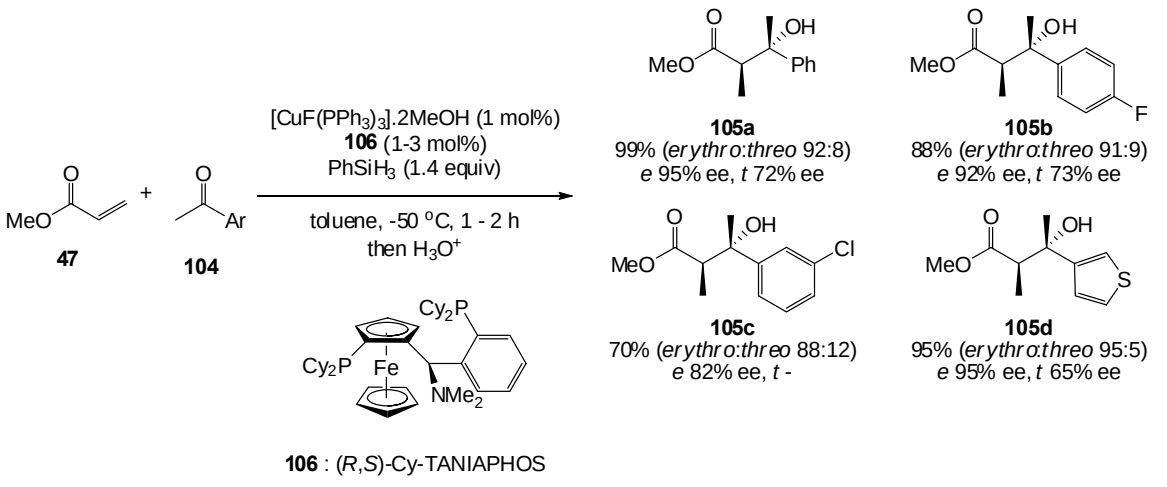
Scheme 29 Synthesis of piperidin-2-ones and piperidines

Lipshutz *et al*. reported the asymmetric reductive cyclisation of β,β'-disubstituted keto-enones, resulting in the generation of 6-membered cyclic products containing three contiguous new stereogenic centres as a single diastereomer with enantiomer excesses of up to 97% (Scheme 30).[50] Yields and selectivities for this impressive transformation were found to be uniformly high and unaffected by the geometry of the enone. The added stereocontrol comes from the formation of the new stereogenic centre after the initial asymmetric conjugate reduction of the enone.



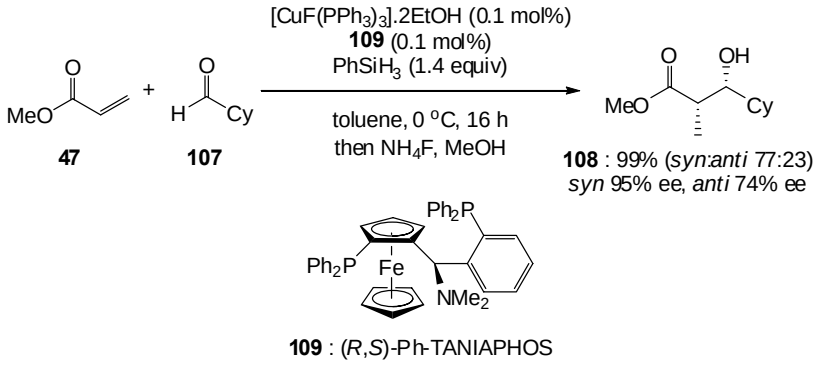
Scheme 30 Reductive cyclisation to give three contiguous asymmetric stereogenic centres

Riant *et al*. used the pre-catalyst $[CuF(Ph_3P)_3].2MeOH$ for the intermolecular asymmetric copper-catalysed reductive aldol reaction; the chiral copper-hydride species was formed from chiral bisphosphine ligands and $PhSiH_3$.[51] A range of chiral bisphosphines was used to couple methyl acrylate and aromatic ketones. Highest diastereo- and enantioselectivities were achieved with (*R*,*S*)-Cy-TANIAPHOS **106**; like all ferrocene based ligands screened, *erythro*-selectivity was observed (Scheme 31).

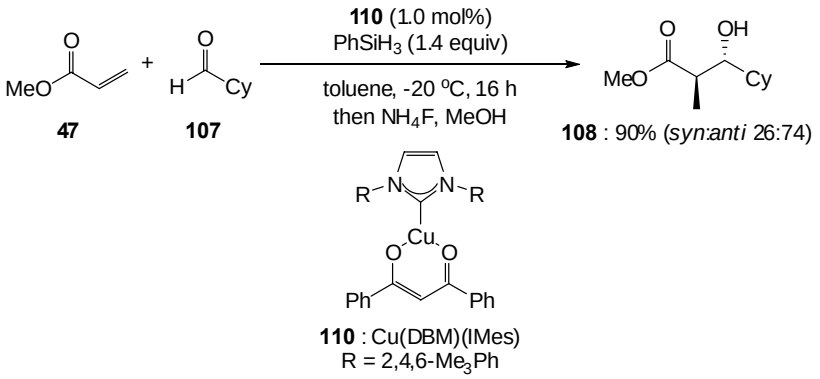


Scheme 31 Reductive coupling of acrylates and aromatic ketones

Further development of this reductive process led to the asymmetric reductive coupling of methyl acrylate and a range of aromatic and aliphatic aldehydes; excellent yields and high enantioselectivities were observed for this *syn*-selective process (Scheme 32).[52] Riant also showed that *anti*-selectivity could be achieved for the same transformation by using the *N*-heterocyclic carbene-copper catalyst **110** (Scheme 33).[53] This process was not limited to methyl acrylate as methyl vinyl ketone and acrylonitrile gave comparable results.

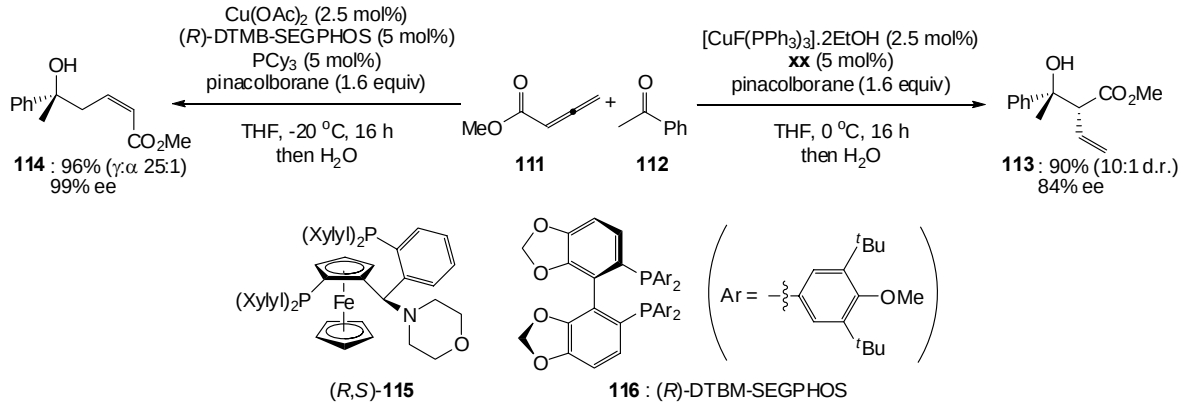


Scheme 32 Riant's *syn*-selective coupling of acrylates and aldehydes



Scheme 33 Riant's syn-selective coupling of acrylates and aldehydes

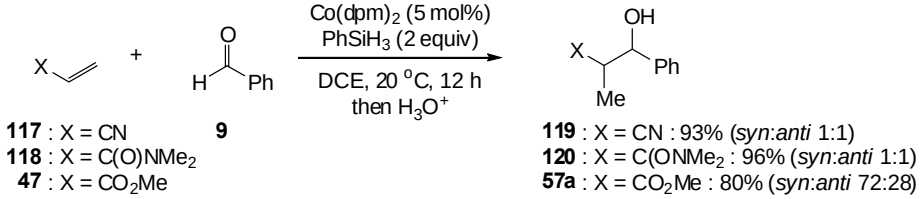
By using pinacolborane as a stoichiometric reductant and switching copper precatalysts and bisphosphine ligands, Shibasaki *et al*. were able to selectively couple allenic esters and ketones either from the α-carbon of the allene, giving the branched product, or the γ-carbon of the allene, giving the linear product (Scheme 34).[54,55] $Cu(OAc)_2$ and (*R*)-DTBM-SEGPHOS **116** gave the γ-aldol product **113** with *cis*-olefin configuration, high enantioselectivities and excellent yields. $[CuF(Ph_3P)_3]$•2EtOH and TaniaPhos **115** gave the α-aldol product **114** with high diastereoselectivity and moderate to high yields with aromatic ketones.



Scheme 34 Enantio- and regioselective reductive coupling of allenic esters and ketones

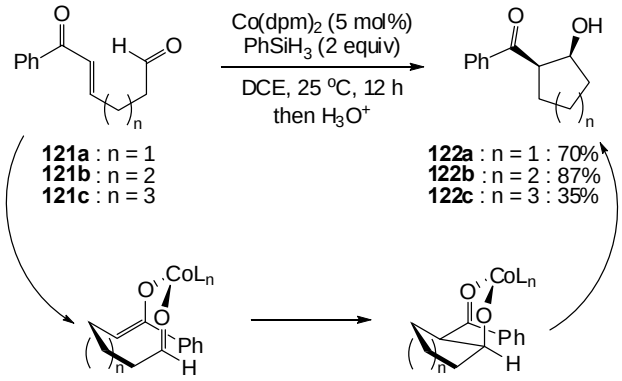
1.2.3 Cobalt-Catalysed Reductive Aldol Reactions

Shortly after Revis and Hilty's original paper on the rhodium-catalysed reduction-aldol reaction,[8] Isayama and Mukaiyama reported a cobalt-catalysed reductive aldol reaction using α,β-unsaturated nitriles, amides and esters.[56] Phenylsilane was used as a hydride source and Co(II)(dpm) was used as a precatalyst, although high yields were observed, selectivity was poor with a *syn*:*anti* of 72:28 being achieved at best (Scheme 35).



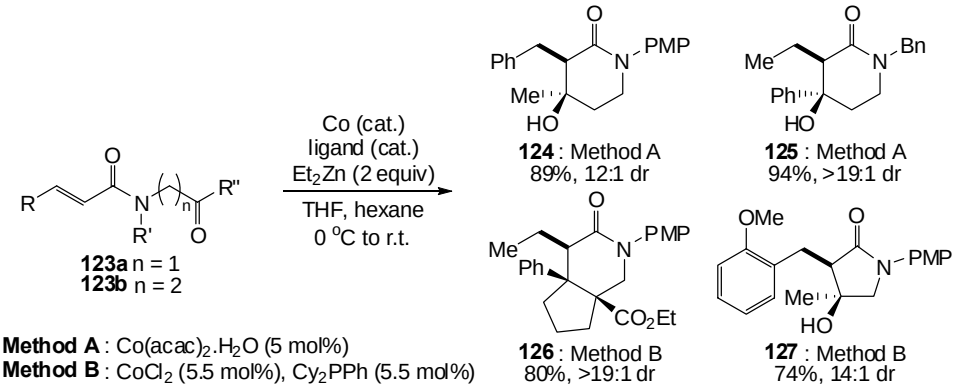
Scheme 35 Cobalt-catalysed reductive aldol reaction

Later, Krische *et al*. employed Isayama and Mukaiyama's cobalt-catalysed reductive conditions in an intramolecular reductive aldol reaction giving five-, six- and seven membered cycloreduction products.[57,58] In contrast to the intermolecular reductive aldol reactions reported by Isayama and Mukaiyama, exceptional *syn*-selectivities (>99:1 for all examples) were reported by Krische *et al*. (Scheme 36). This has been explained on the basis of a Zimmerman-Traxler type transition state.



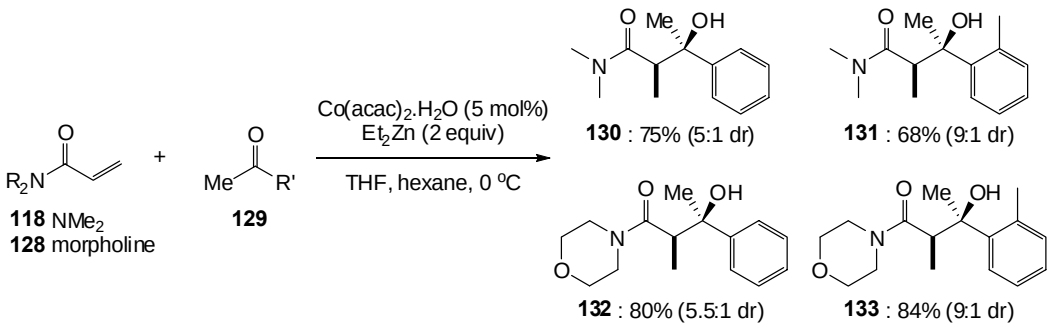
Scheme 36 Intramolecular cobalt-catalysed reductive aldol reaction

Lam *et al*. investigated a cobalt-catalysed alternative to their diastereo- and enantioselective copper-catalysed synthesis of β-hydroxylactones and β-hydroxylactams.[59] A variety of stoichiometric reductants were screened, hydrosilanes gave complex reaction mixtures while, after investigating organometallic reagents with β-hydride-containing alkyl groups (Et_3B and Et_2Zn),[60-65] efficient reductive cyclisation occurred with the use of diethylzinc. High yields and diastereoselectivities were observed with $Co(acac)_2$ hydrate when forming 4-hydroxypiperidin-2-ones and $CoCl_2$ ligated with Cy_2PPh was found to be an effective catalyst system with substrates **123a** and **123b**; these showed incomplete conversion with $Co(acac)_2$ hydrate (Scheme 37).

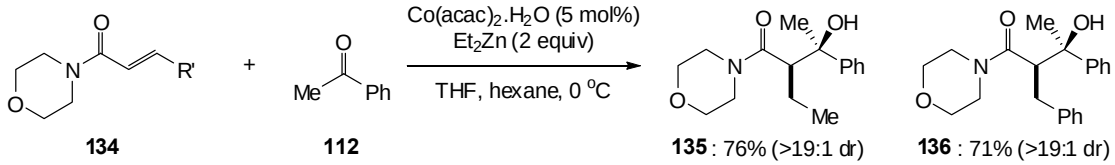


Scheme 37 Cobalt-catalysed reductive aldol reaction mediated by Et_2Zn

This cobalt-catalysed reductive aldol reaction was not found to be limited to intramolecular transformations, both *N*,*N*'-dimethylacrylamide **118** and 4-acryloylmorpholine **128** were coupled with aliphatic, aromatic and heteroaromatic ketones.[66] Moderate diastero-selectivities were observed, however, *ortho*-substitution on acetophenone derivatives promoted selectivity to 9:1 (Scheme 38). β-Substitution on the olefin resulted in a large elevation in the diastereoselectivity, with **135** and **136** being accessed with diastereoselectivities of >19:1 (Scheme 39).

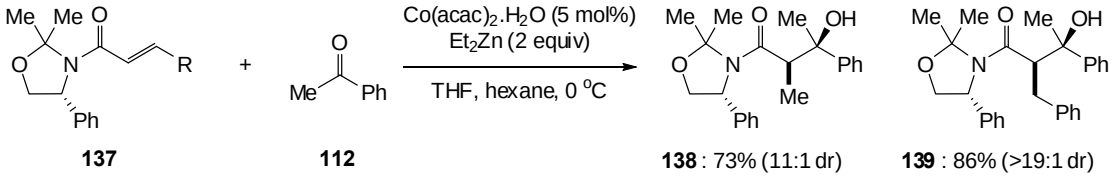


Scheme 38 Intermolecular cobalt-catalysed reductive aldol reaction



Scheme 39 Reductive aldol reaction using β-substituted acrylamides

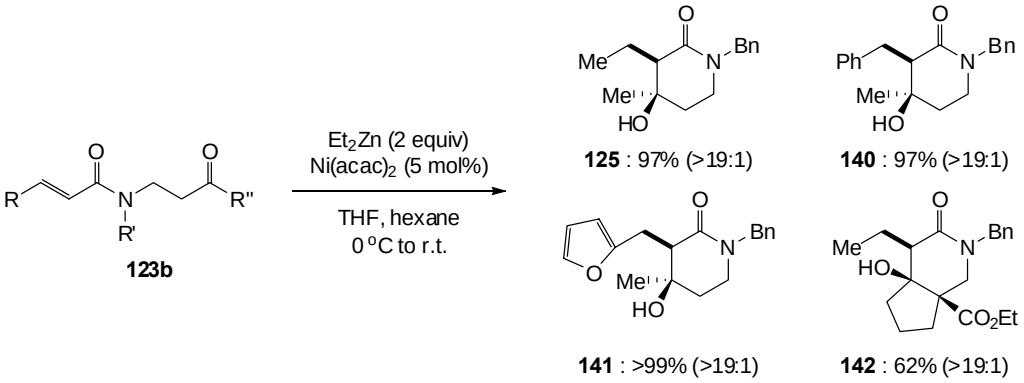
To develop an asymmetric variant of this reaction Lam turned to a chiral auxiliary strategy; ligation of cobalt was not an option for asymmetric induction due to it being a zinc-, not a cobalt-, enolate involved in the key carbon-carbon bond forming step.[67] *N*-Acryloyloxazolidine **137** was identified as a suitable substrate reacting with acetophenone to give the aldol product **138** in 73% yield and with a 11:1 diastereoselectivity. A range of aromatic and heteroaromatic ketones revealed the aldol product in moderate yields (58-76%) and good diastereoselectivities (up to 13:1); as with α,β-unsaturated morpholine amides (Scheme 39), substitution on the β-carbon improved reaction yields and selectivities (Scheme 40).



Scheme 40 Cobalt-catalysed reductive aldol reaction controlled by a chiral auxiliary

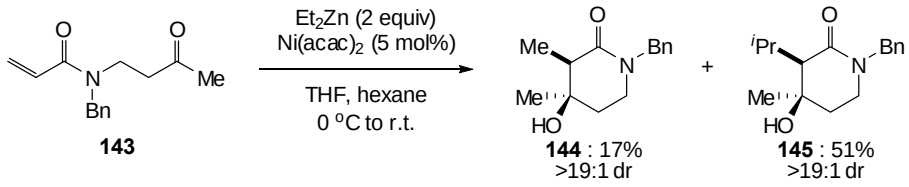
1.2.4 Nickel-Catalysed Reductive Aldol Reactions

Alongside the cobalt catalysis described above, Lam developed a complementary nickel catalysed intramolecular reductive aldol reaction forming β-hydroxylactams and β-hydroxylactones, again using a diethylzinc as a stoichiometric reductant.[68] This nickel-catalysed reductive aldol reaction showed higher reactivity than the cobalt system; substrates which had previously shown little or no reactivity now gave the desired products (Scheme 41).



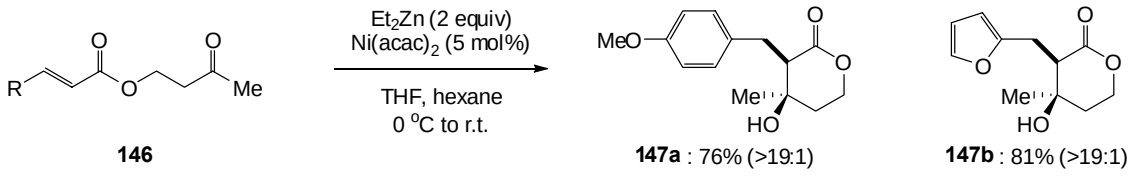
Scheme 41 Nickel-catalysed reductive aldol reaction mediated by Et_2Zn

A problem encountered with this nickel system is that of competitive alkylative aldol reaction, a side reaction which is not observed under cobalt catalysis. Substrate **143** gave reductive aldol product **144** in 17% yield and alkylative aldol product **145** in 51% yield (Scheme 42). Lam found that this competitive alkylation is eliminated by the addition of α- or β-substituents on the acrylamide.



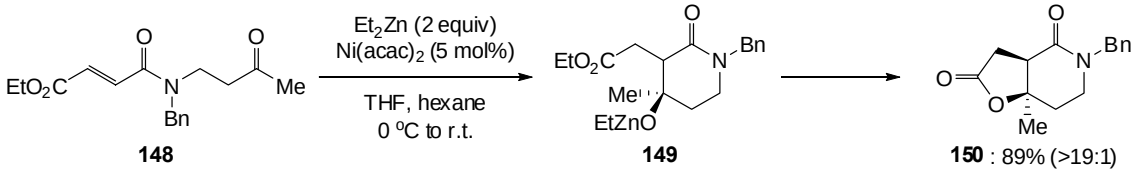
Scheme 42 Competative alkylative aldol reaction

The synthesis of six-membered β-hydroxylactones was also successful under nickel catalysis, a transformation which was found not to be possible under the comparable cobalt reductive conditions; the results observed were comparable to those shown with the keto-acrylamides (Scheme 43). However, a significant quantity of the alkylative aldol product was observed with electron-deficient substrates.

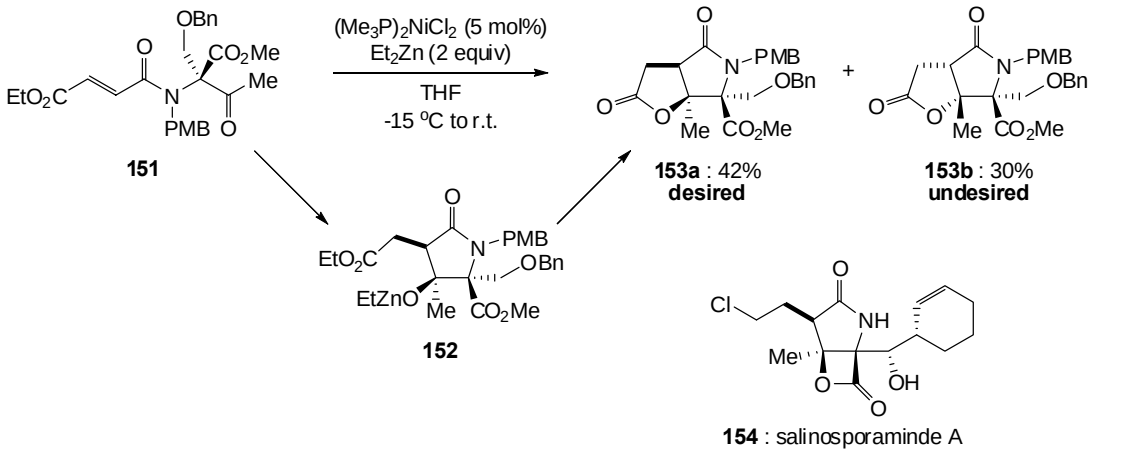


Scheme 43 β-Hydroxy lactone synthesis

In this initial study into nickel catalysis, Lam *et al*. observed the formation of bicyclic product **150**, a product of the zinc alkoxy aldol product **149** undergoing lactonisation (Scheme 44). Following this observation Lam *et al*. carried out a formal synthesis of salinosporamide A **154**, a potent 20S proteasome inhibitor and anti-cancer compound.[69] Formation of the β-hydroxy-γ-lactam core of **154** required the reductive cyclisation-lactonisation of **151**, a much more highly functionalised precursor than previously used. Bicyclic **153a** was isolated in 42% yield and was transformed, in a number of steps, to salinosporamide A **154** (Scheme 45).

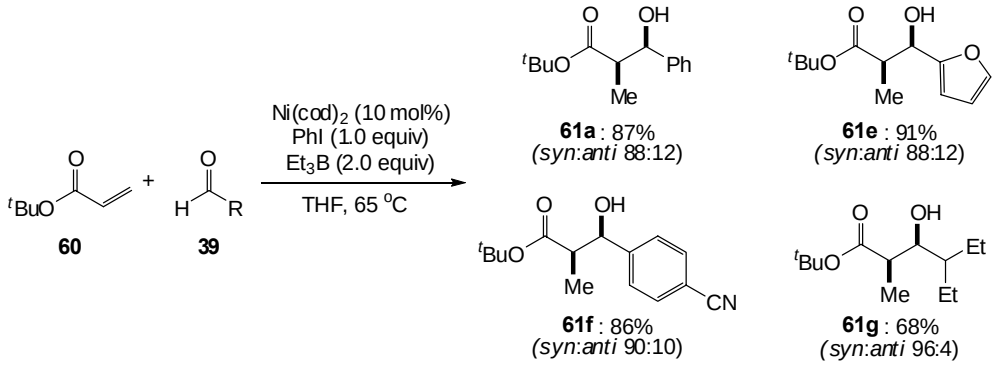


Scheme 44 Reductive aldol-lactonisation



Scheme 45 Nickel-catalysed reductive aldol-lactonisation reaction, a key step in the synthesis of **154**

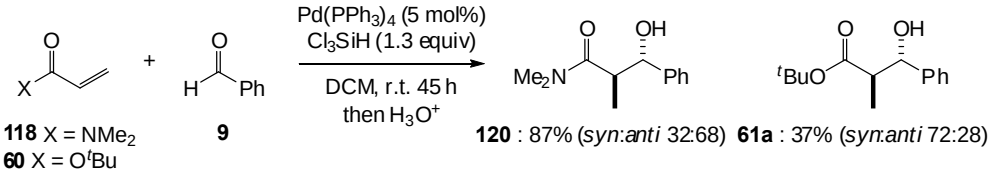
Prior to work done by Lam *et al*. on the nickel-catalysed reductive aldol cyclisation, Chrovian and Montgomery reported a similar system in which triethylborane was used as the terminal reductant.[70] The reaction was found to be initiated by phenyl iodide and only 5% of the Michael aldol side-product was observed. High yield and *syn*-selectivity was observed for this process with a range of aldehydes (Scheme 46).



Scheme 46 Nickel-catalysed reductive aldol reaction mediated by BEt_3

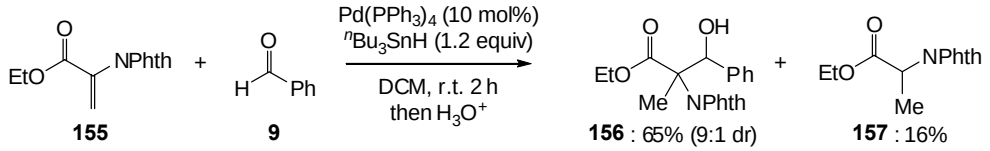
1.2.5 Palladium-Catalysed Reductive Aldol Reactions

Little work has been carried out on tandem reductive processes initiated by a palladium-catalysed conjugate reduction. In a rare example, Kiyooka *et al*. illustrated the substrate dependence of the palladium-catalysed reductive aldol reaction. *Anti*-selectivity (*syn*:*anti* 32:68) was observed in the coupling of *N*,*N*'-dimethylacrylamide **118** with benzaldehyde **9**, whereas, *syn*-selectivity (*syn*:*anti* 72:28) was observed when using *tert*-butyl acrylate **60** with a significant depletion of yield (Scheme 47).[71]



Scheme 47 Palladium-catalysed reductive aldol reaction

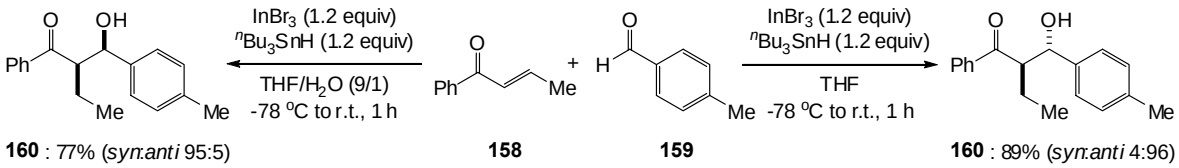
A further example comes from an investigation into the application of dehydroamino acid derivatives in tandem processes. A palladium-catalysed reductive aldol reaction was achieved using *n*-Bu_3SnH as a hydride donor, *N*-phthaloyl dehydroalanine **155** and benzaldehyde **9** gave a mixture of **156** and **157** (Scheme 48).[72]



Scheme 48 Reductive coupling of *N*-phthaloyl dehydroalanine and benzaldehyde

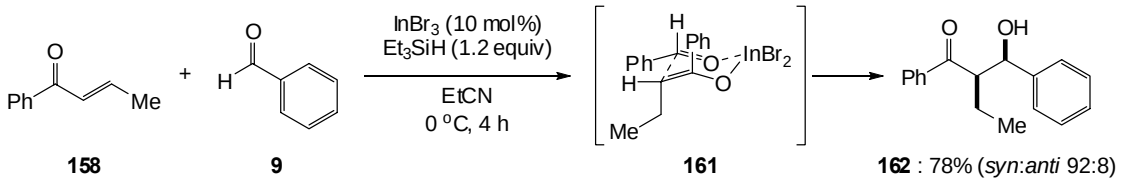
1.2.6 Indium-Catalysed Reductive Aldol Reactions

As with palladium-catalysis, there are few reports of indium-catalysed reductive aldol reactions; however, those few reports disclose highly selective processes. Baba *et al*. used stoichiometric amounts of $InBr_3$ with *n*-Bu_3SnH for the reductive aldol reaction between enones and aromatic aldehydes.[73] Interestingly, selectivity could be switched by the addition of water to the solvent system (Scheme 49). When carried out in anhydrous THF the thermodynamically favourable product was observed (*syn*:*anti* 4:96); addition of water to the solvent system (THF/H_2O : 9/1) led to the kinetically favourable product (*syn*:*anti* 95:5).



Scheme 49 Indium-promoted reductive aldol reaction

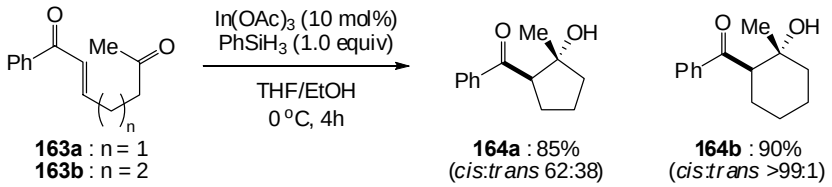
Baba *et al*. showed that sub-stoichiometric amounts of $InBr_3$ could be used in conjuction with triethylsilane; this led to excellent *syn*-selectivity (typically *syn*:*anti* >99:1) with aromatic aldehydes and enones.[74] This high *syn*-selectivity can be attributed to the formation of a (*Z*)-indium enolate as conjugate reduction occurs to the *s-cis* configured enone.



Scheme 50 Indium-catalysed reductive aldol reaction

Adding to the findings of Baba *et al*., Miura and Hosomi reported the indium-catalysed conjugate reduction and reductive aldol reaction using $In(OAc)_3$ and $PhSiH_3$.[75] Reported yields were comparable to those reported by Baba while selectivity was lower for the

reductive coupling of aryl aldehydes and enones. However, these conditions were adapted for the intramolecular reductive aldol reaction of **163a** and **163b**. Complete stereocontrol was observed with the six-membered product **164b**, while **163a** gave five-membered **164a** as a 62:38 ratio of the *cis*:*trans* isomers (Scheme 51).

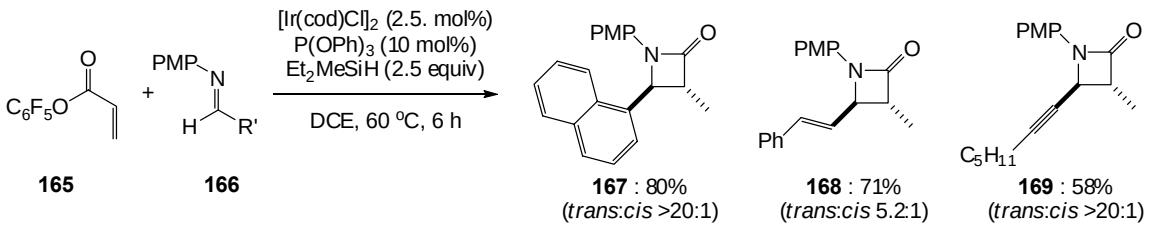


Scheme 51 Indium-catalysed intramolecular reductive aldol reaction

1.3 Reductive Mannich Reactions

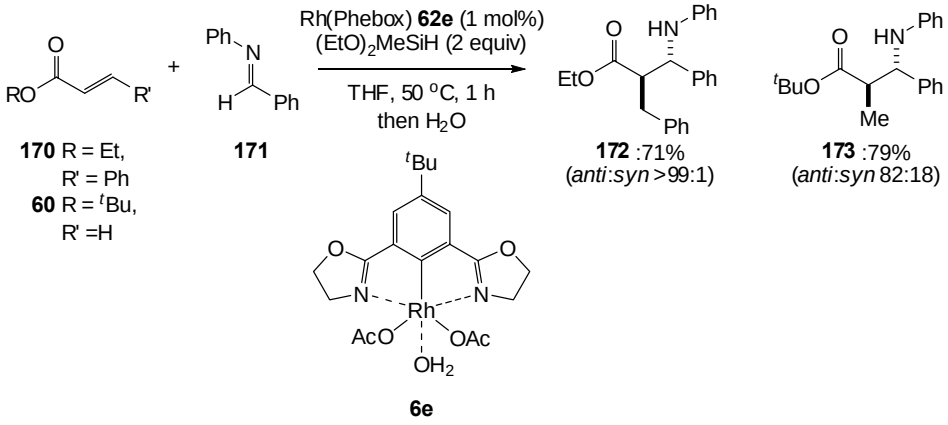
Reductive Mannich reactions offer an efficient route to β-amino esters, which are excellent intermediates in the synthesis of β-amino acids and β-lactams. This challenging transformation requires anhydrous conditions and needs to avoid competitive imine reduction. The majority of examples of reductive Mannich reactions involve the reductive coupling of Michael acceptors to aldimines.

Following a two-step synthesis of β-lactams *via* a reductive Mannich reaction reported by Isayama,[56] Morken *et al*. reported the synthesis of β-lactams *via* an iridium-catalysed reductive Mannich reaction.[76] Under the reductive conditions the Mannich product is cyclised to give the β-lactam in high yields and *trans*-selectivity. Yields were significantly higher with pentafluorophenyl acrylate; a yield of only 13% was observed with phenyl acrylate (Scheme 52).



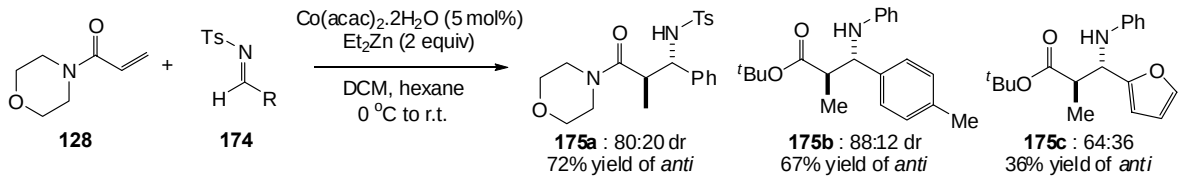
Scheme 52 Iridium-catalysed β-lactam synthesis

Aldimines were coupled with methyl acrylate using a cationic rhodium complex [Rh(COD){P(OPh)$_3$}$_2$]OTf and Et$_2$MeSiH by Matsuda.[77] This synthesis of β-amino esters occurs with slight *anti*-selectivity and high to excellent yields; highest yields were observed with *N*-tosylaldimines. Greater diastereoselectivity was achieved by Nishiyama *et al*. who applied their Rh(Phebox) ligands to the reductive Mannich reaction which, although gave high yields and moderate diastereoselectivities, did not result in any enantioselectivity being observed when a chiral Rh(Phebox) complex was used.[78] Excellent *anti*-selectivity was achieved when coupling cinnamate **170** and aldimine **171**; such high selectivity was not observed with *tert*-butyl acrylate **60** (Scheme 53).



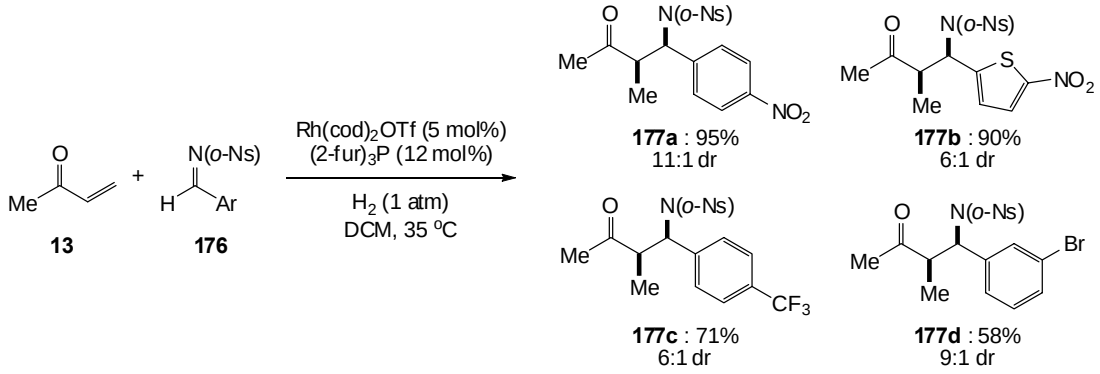
Scheme 53 Rh(Phebox)-catalysed reductive Mannich reaction

Lam applied the cobalt-catalysed conditions developed for the reductive aldol reaction, using diethylzinc as a stoichiometric reductant,[59,66] to the coupling *N*-tosylaldimines **174** with 4-acryloylmorpholine **128**.[79] Moderate to good yields and diastereomeric ratios of up to 88:12 (*anti*:*syn*) were observed for the transformation which proceeds *via* a zinc enolate (Scheme 54).



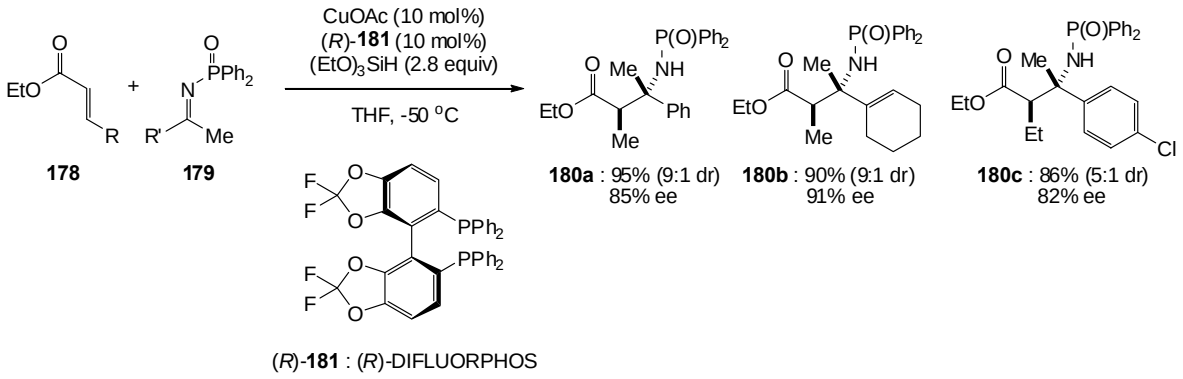
Scheme 54 Cobalt-catalysed reductive Mannich reaction

After the success of the molecular hydrogen mediated reductive aldol reaction (*cf*. 1.2.1.2),[5] Krische reported the rhodium-catalysed reductive Mannich coupling of vinyl ketones to *N*-sulfonylimines mediated by hydrogen.[80] Using the same conditions as the reductive aldol chemistry the reductive coupling of methyl vinyl ketone and *N*-arylaldimides gave the Mannich products in excellent yields (88-99%) but with poor diastereoselectivity (<2:1 dr). To overcome the problem of poor selectivity, caused by the facile geometrical isomerisation of the *N*-arylaldimine in the presence of rhodium,[81,82] *N*-sulfonylimines were employed as the reaction electrophile as they are conformationally more stable. Attention was turned to the coupling of vinyl ketones and *N*-(o-nitrobenzenesulfonyl)imines **176** due to the ease of deprotection of the Mannich adducts. Good yields and excellent *syn*-diastereoselectivities were observed (Scheme 55).



Scheme 55 Diastereoselective hydrogen-mediated reductive Mannich reaction

The only example of transition metal catalysed reductive Mannich reactions to ketimines comes from Shibasaki *et al*. who coupled acrylates with *N*-diphenylphosphinoyl ketimines **179** under copper catalysis.[83] Initial efforts focused on diastereoselective reductive Mannich reactions. Pinacolborane was used as a stoichiometric reductant and triphenylphosphine as a ligand; excellent yields (up to 94%) and diastereoselectivities (up to 99:1) were observed. The high yields and diastereoselectivities remained on addition of (*R*)-DIFLUORPHOS **181** which, with $(EtO)_3SiH$, gave the β-amino acids with high enantiomeric excess (Scheme 56). Acid hydrolysis of the diphenylphosphinoyl group gave the free amine with no racemisation or epimerisation.

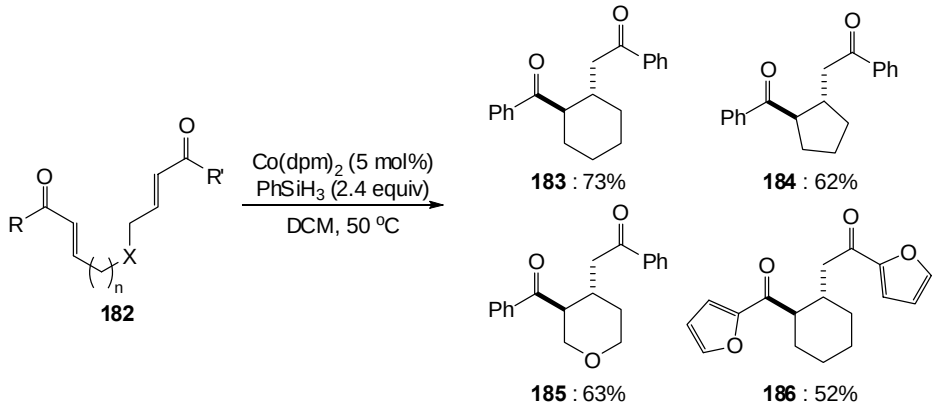


Scheme 56 Reductive Mannich reaction of acrylates and ketimines

1.4 Reductive Michael Reactions

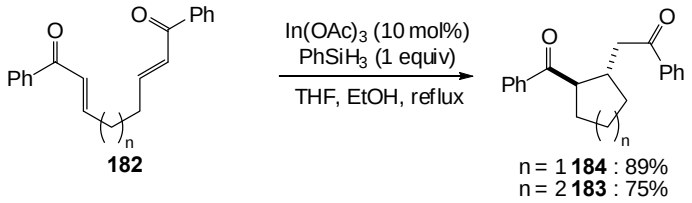
Only two reductive systems have been applied to the reductive Michael reaction, both these intramolecular transformations observe complete *trans*-selectivity of the cyclic products from bis-enones.

Krische *et al*. reported the cobalt-catalysed intramolecular reductive Michael reaction of bis(enones).[3,57,58] Interestingly, this reaction gave only the *trans*-cyclic products in moderate to high yields, a switch in selectivity compared to the related intramolecular reductive aldol reaction. This reaction worked well for symmetrical bis-enones and tolerated heteroatoms in the carboskeleton, which led to the synthesis of cyclic ether **185** (Scheme 57); however, chemoselectivity was poor using non-symmetrical substrates.



Scheme 57 Cobalt-catalysed reductive Michael reaction

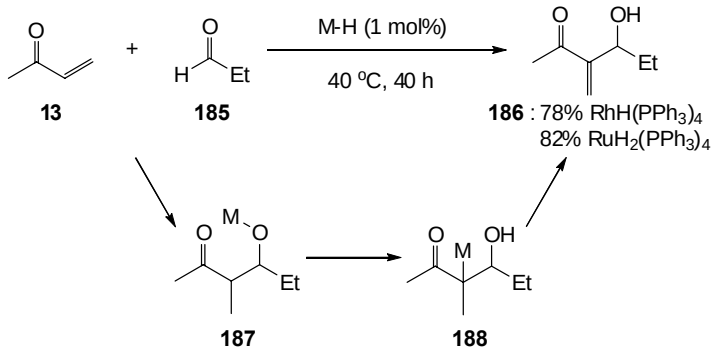
Miura and Hosomi's conditions for the indium-catalysed intramolecular reductive aldol reaction (*cf*. 1.2.6) also were applicable to the related reductive Michael reaction.[75] Like Krische, Miura and Hosomi observed complete *trans*-selectivity, with products being isolated in high yields (Scheme 58).



Scheme 58 Indium-catalysed reductive Michael reaction

1.5 Morita-Baylis-Hillman Type Reactions

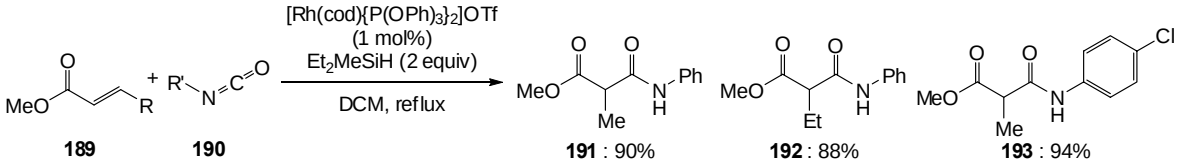
Matsuda *et al*. reported the synthesis of Morita-Baylis-Hillman type products from Michael acceptors and aldehydes.[84-86] The process, catalysed by 1 mol% of either $RhH(PPh_3)_4$ or $RuH_2(PPh_3)_4$, involves the formation of metal-aldolate **187**. **187** undergoes tautomerisation to **188** and subsequent β-hydride elimination, regenerating the metal-hydride species, to give the Morita-Baylis-Hillman type product **186** (Scheme 59).



Scheme 59 Synthesis of Morita-Baylis-Hillman type products initiated by conjugate reduction

1.6 Hydrocarbamoylation Reactions

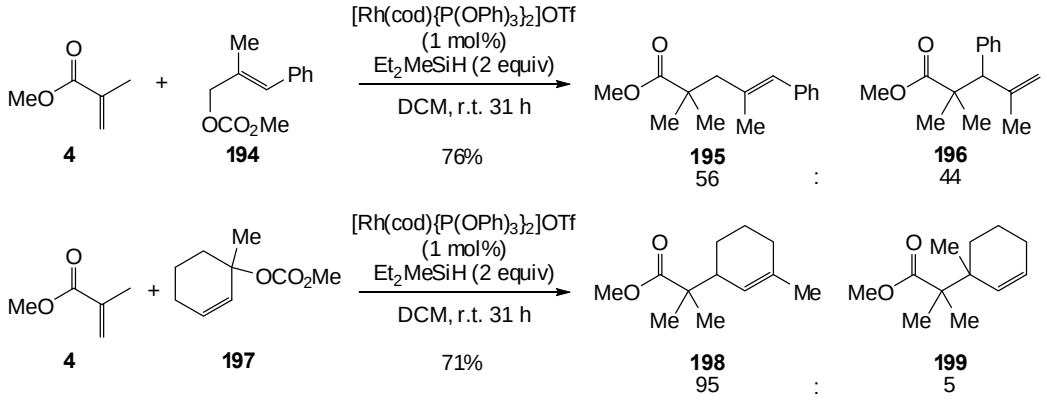
Matsuda *et al*. showed aryl isocyanates to be useful coupling partners for rhodium-enolates formed from the hydrometallation of α,β-unsatrurated esters.[87] The hydrocarbamoylation products were formed in high yields regardless of substitution of the Michael acceptor or the aryl isocyanate (Scheme 60). No isocyanate reduction was observed.



Scheme 60 Rhodium-catalysed hydrocarbamoylation

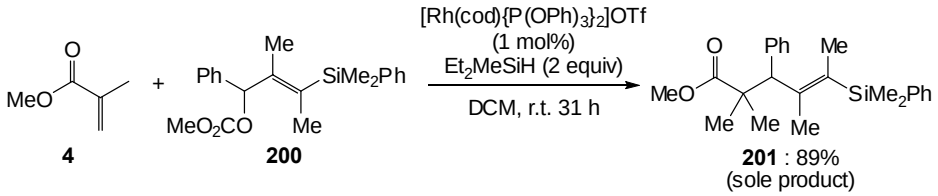
1.7 Hydroallylations

Matsuda *et al*. carried out the rhodium-catalysed hydroallylation of Michael acceptors to give γ,δ-unsaturated esters in high yields by reductive coupling of acrylates and allylic carbonates.[88,89] Initial studies showed that regioselectivity was poor unless one terminus was sterically disfavoured, for example allylic carbonyl **194** gave **195** and **196** as a 56:44 mixture, whereas, hydroallylation using **197** resulted in a 95:5 mixture of the two regioisomers (Scheme 61).



Scheme 61 Rhodium-catalysed hydroallylation

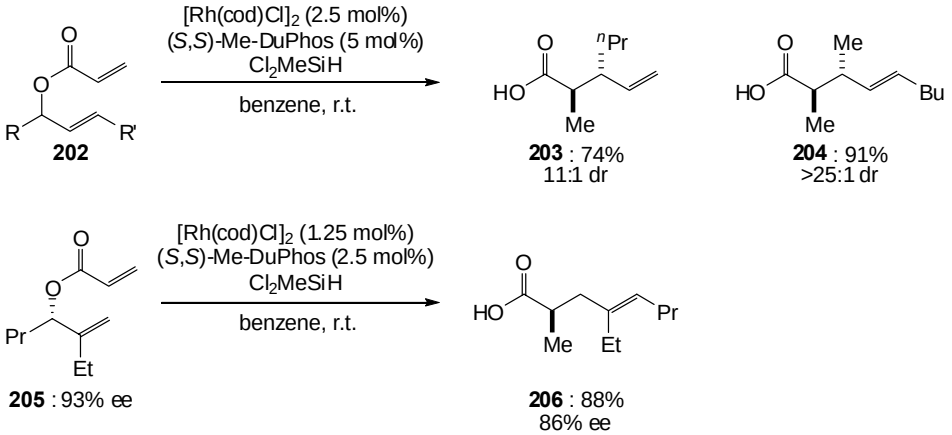
To develop this regioselective process further, Matsuda *et al*. introduced triorganosilyl groups to either end of the allylic termini of the allylic carbonate (Scheme 62).[89] Regioselectivities and yields were uniformly excellent using silylated allylic carbonates. Acidic protodesilylation proceeded in moderate yields.



Scheme 62 Hydroallylation using silylated allylic carbonates

1.8 Reductive Claisen Rearrangements

The reductive Claisen rearrangement was reported by Morken and Miller.[90] Substituted allyl acrylates underwent rhodium-catalysed hydrosilylation and subsequent Ireland-Claisen rearrangement to give γ,δ-unsaturated carboxylic acids in good yields and diastereoselectivities (Scheme 63). The reductive Claisen rearrangement of chiral substrate **205** proceeded with little drop in enantiopurity. Product **206** was used as a key intermediate in the total synthesis of inostamycin (*cf*. 1.2.1.3).[27]



Scheme 63 Rhodium-catalysed reductive Claisen reaction

1.9 References

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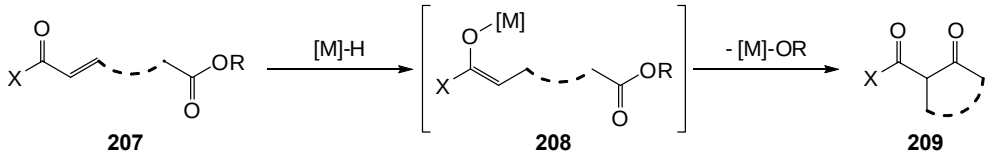
Chapter 2 - Initial Studies into the Reductive Dieckmann Condensation

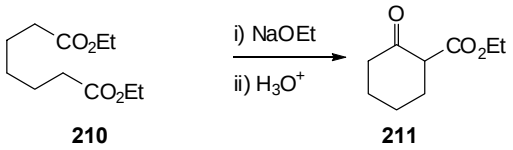
2.1 Dieckmann Condensation

As discussed in chapter 1, catalytic tandem reductive processes have been of great interest over the last two decades. Of particular interest is the use of Michael acceptors as latent enolates enabling reductive aldol, Mannich and Michael reactions to take place. However, to our knowledge there have been no examples of a reductive Dieckmann (or Claisen) condensation in which enolate **208**, formed after hydrometallation, attacks the ester, eliminating an alkoxylate group to give a 1,3-dicarbonyl product **209** (Scheme 64).



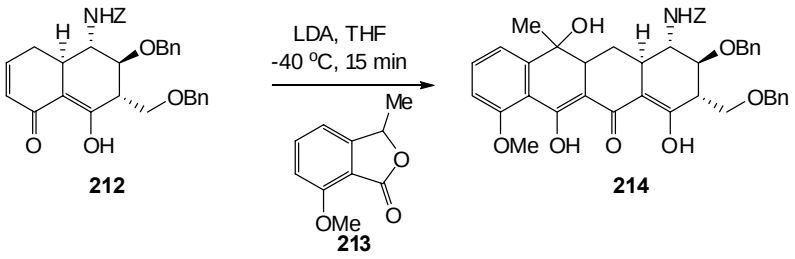
Scheme 64 Proposed reductive Dieckmann condensation

The Dieckmann condensation, an intramolecular variant of the Claisen condensation, is a convenient route into the formation of β-keto esters by treatment of a diester with strong base, typically sodium alkoxide (Scheme 65).[1]



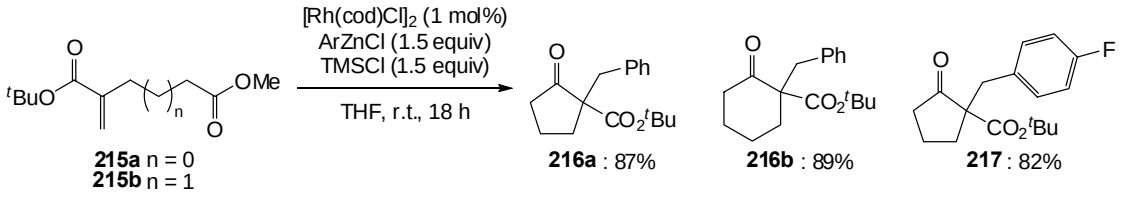
Scheme 65 Dieckmann condensation

Although there are no examples of reductive Dieckmann condensations, comparable Michael Dieckmann condensations have been reported. For example, a key step in the synthesis of natural product (+/-)-napyradiomycin A1 **214** is the Michael Dieckmann condensation of **212** with isobenzofuranone **213** (Scheme 66).[2]

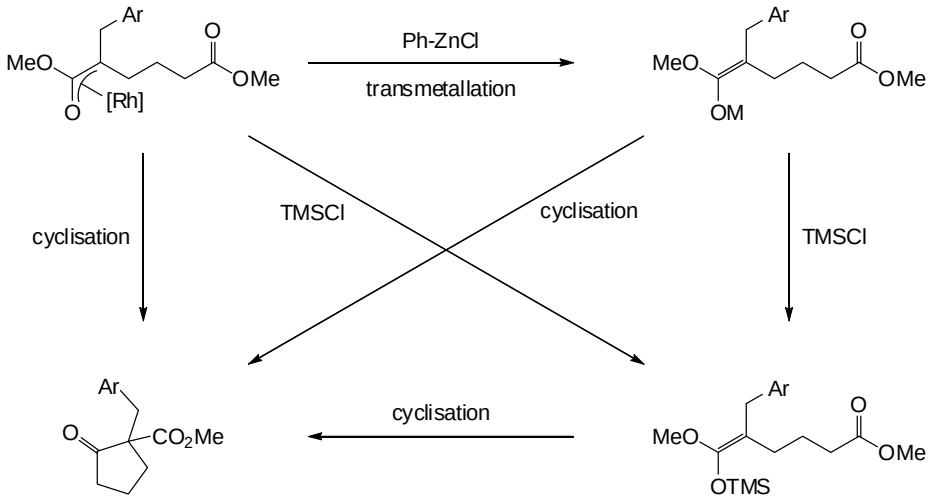


Scheme 66 Michael Dieckmann condensation as a key step towards the synthesis of (+/-)-napyradiomycin

More recently, Frost *et al*. have reported the tandem rhodium-catalysed Michael Dieckmann condensation as a route to β-keto esters containing an all-carbon quaternary centre at the α-carbon.[3,4] In their initial study, five- and six-membered β-keto esters were formed by the rhodium-catalysed conjugate addition of arylzinc chlorides to α-substituted acrylic esters **215a** and **215b** (Scheme 67). The reaction pathway is unclear with a number of possible routes proposed (Scheme 68).

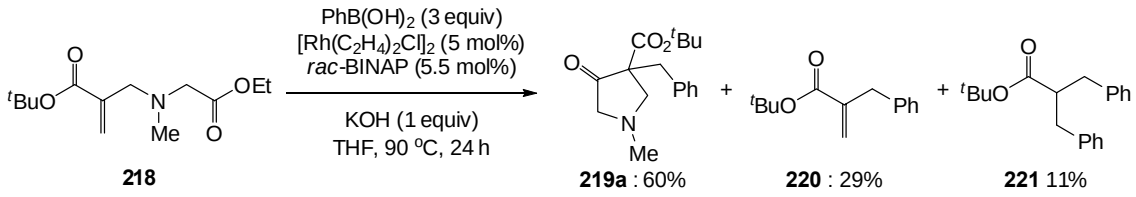


Scheme 67 Rhodium-catalysed Michael Dieckmann condensation



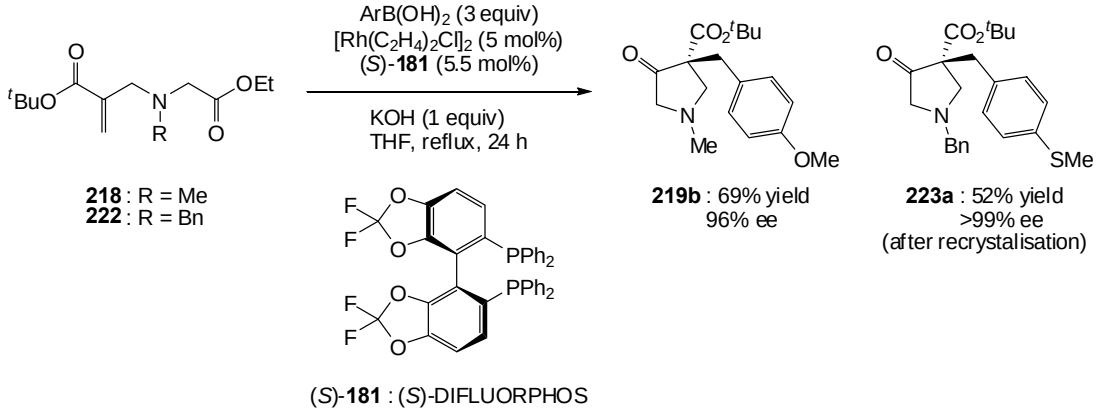
Scheme 68 Plausible reaction pathways for Frost's Michael Dieckmann reaction

To develop this elegant methodology further, Frost *et al*. introduced a heteroatom into the carbon backbone of the α-substituted acrylic ester, enabling the synthesis of 3,3'-disubstituted 4-oxopyrrolidines containing an all carbon quaternary centre.[4] The rhodium-catalysed addition of aryl boronic acids to acrylate **218**, derived from sarcosine ethyl ester, was carried out. The desired Michael Dieckmann product **219** was found to be the major product of this process (Scheme 69). An addition/elimination reaction also occurs under these conditions giving acrylate **220**, which can also undergo a Michael addition by a second equivalent of aryl boronic acid to give **221** (Scheme 69).



Scheme 69 Rhodium-catalysed synthesis of 3,3'-disubstituted 4-oxopyrrolidines

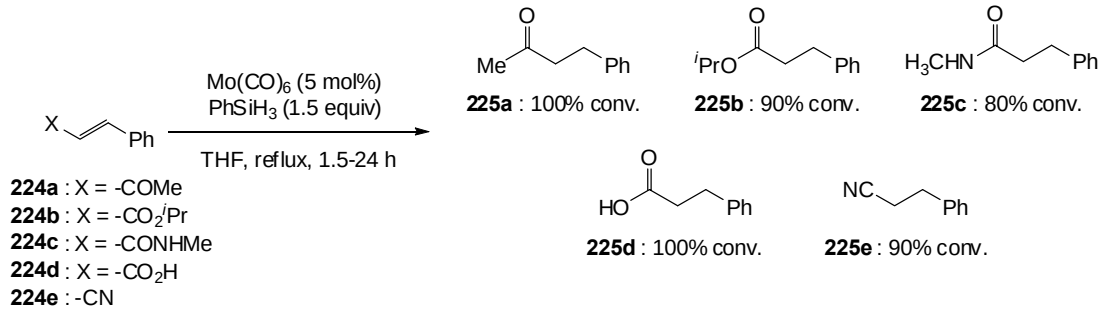
After initial studies into the rhodium-catalysed Michael Dieckmann condensation attention was then turned to asymmetric induction at the all-carbon quaternary centre by the introduction of a chiral ligand. After screening a range of chiral bisphosphines (*S*)-DIFLUORPHOS **181** was found to be the most effective ligand giving 3,3'-disubstituted 4-oxopyrrolidine **219b** in a 69% yield and an excellent 96% ee (Scheme 70). The absolute stereochemistry of **223a** was found to be *R* by X-ray crystallography.



Scheme 70 Asymmetric rhodium-catalysed Michael Dieckmann condensation

2.2 Molybdenum-Catalysed Conjugate Reduction

Amongst the vast array of conjugate reduction literature is Keinan's 1987 report on the molybdenum-catalysed conjugate reduction of Michael acceptors,[5] a paper which has received little attention since publication. In this report, a number of Michael acceptors were reduced by molybdenum hexacarbonyl using phenylsilane as the terminal reductant (Scheme 71). By ^{1}H NMR and isotope labelling studies, Keinan showed the process proceeded *via* a silyl enol ether which was protonated on addition of water at the end of the reaction. Excellent conversions were observed for the reduction of α,β-unsaturated ketones, esters, amides, nitriles and carboxylic acids (75-100% conversion determined by GC and ^{1}H NMR analysis).



Scheme 71 Keinan's molybdenum-catalysed conjugate reduction

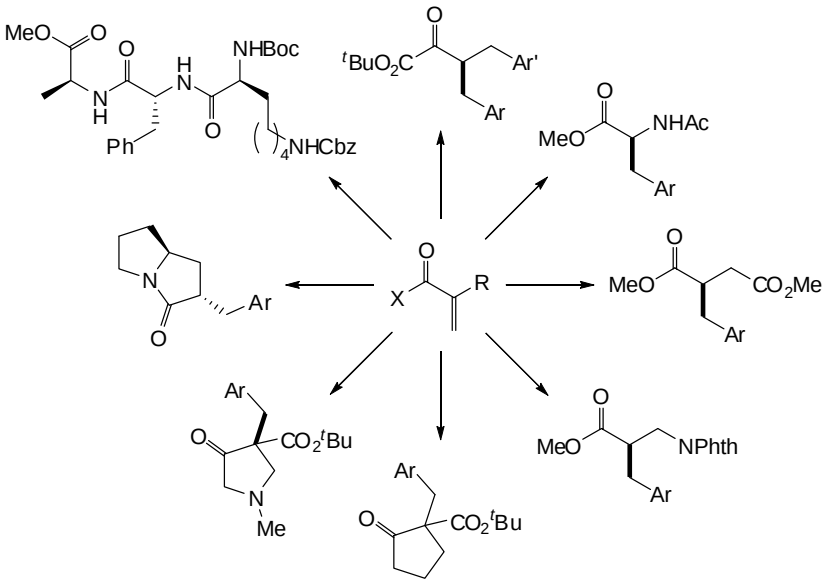
It is the availability and low cost of $Mo(CO)_6$ which makes it an attractive catalyst for organic transformations. $Mo(CO)_6$ has many applications within organic chemistry. $Mo(CO)_6$ can be converted into a range of molybdenum complexes by replacement of its carbonyl ligands by both π- and σ-donor ligands, but it can also be used as a catalyst in its own right.[6] Beyond its use as a safe, convenient source of carbon monoxide,[7-24] $Mo(CO)_6$ has been used in asymmetric allylic alkylations,[25] alkyne metathesis,[26,27] Pauson-Khand reactions,[28,29] allenic Pauson-Khand reactions,[30-32] [2+2] cyclisation,[33] N-O bond reduction,[34-40] cycloisomerisations[41-44] and conjugate reduction.[5]

The catalytic activity of molybdenum depends on the ease in which coordinatively saturated $Mo(CO)_6$ is converted to coordinatively unsaturated $Mo(CO)_{6-n}$. Typically this is achieved thermally[45] or photochemically.[46-51] On investigating the thermal displacement of

carbonyl ligands from $Mo(CO)_6$, Keinan showed that, although rapid activation occurs in diglyme between 90-100 ^oC, efficient activation of $Mo(CO)_6$ can be achieved in THF at reflux.[5] It was also noted that catalytic activity significantly depended on the physical removal of carbon monoxide from the reaction mixture; reactivity was retarded when the reaction was carried out in a sealed vessel.

2.2.1 α-Substituted Acrylic Esters

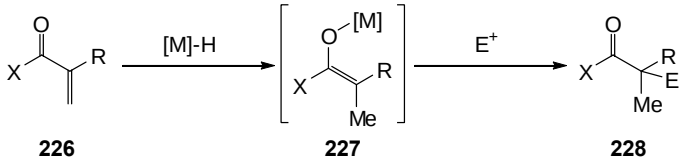
Of interest to the Frost group is the functionalisation of α-substituted acrylic esters and α-substituted acrylic amides through rhodium-catalysed conjugate additions. Frost has shown that these challenging substrates can be used in the preparation of 2-alkylsuccinates, both α- and β-amino acid derivatives, 2-benzyl pyrrolizidinones, β-keto esters, α,α'-dibenzyl esters and in peptide modifications (Scheme 72).[3, 52-60]



Scheme 72 Array of products synthesised from α-substituted acrylate esters by the Frost *et al.*

2.2.2 Conjugate Reduction of α-Substituted Acrylic Esters

The use of α-substituted Michael acceptors in catalytic tandem reductive processes is a potential route to enantiomerically enriched all-carbon quaternary centres (Scheme 73).



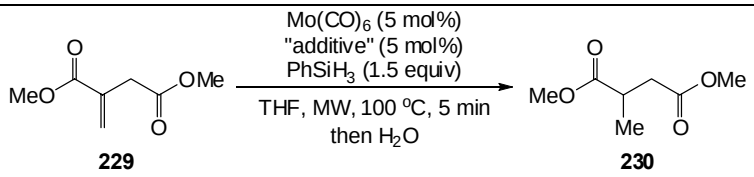
226 **227** **228**

Scheme 73 The use of α-substituted acrylic esters in tandem reductive processes

To investigate the reduction of α-substituted acrylic ester, readily available dimethyl itaconate (DMI) **229** was used as a model substrate. Reduction of DMI was carried out using Keinan's molybdenum-catalysed conjugate reduction reagents under microwave irradiation. It was found that after 10 minutes at 100 ^{o}C, complete conversion to dimethyl 2-methylsuccinate **230** was observed, with a 60% conversion being observed after a period of 5 minutes (Table 1, entry 1). With this result in hand, an additive screen was performed in an attempt to improve the activity of the reductive system. In this regard, 5 mol% of additive was added to the reaction mixture which was heated to 100 ^{o}C for 5 minutes (Table 1).

A range of additives was screened and the reaction was either retarded or completely shut down by the addition of both Lewis acids and Lewis bases (Table 1, entries 2-10). However, great success was observed on the addition of *N*-methylmorpholine *N*-oxide (Table 1, entry 11). As discussed above (*cf*. 2.2), it is the removal of the carbonyl ligands from $Mo(CO)_6$ and subsequent removal of carbon monoxide from the atmosphere which is key to the activation of the molybdenum catalyst. It is therefore unsurprising that the oxidative removal of the carbonyl ligands from $Mo(CO)_6$ by *N*-methylmorpholine *N*-oxide (NMO) greatly increases the rate of reaction for conjugate reduction of DMI.

Table 1 Additive screen for the molybdenum-catalysed reduction of DMI



entry	additive	conversion, %[b]
1	no additive	60
2	DMAP	0
3	$CyNH_2$	0
4	triethylamine	18
5	L-Proline	17
6	binaphthyl-2,2'-diyl hydrogen phosphate	17
7	BINOL	55
8	boric acid	33
9	BINAP	0
10	DMSO	20
11	**NMO**	**100[c]**

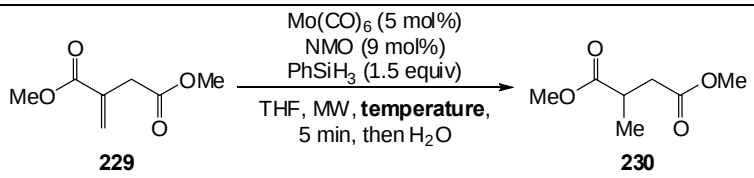
[a] Reaction conditions: DMI (1 equiv), $Mo(CO)_6$ (5 mol%), additive (5 mol%), $PhSiH_3$ (1.5 equiv), THF (1 mL); reaction mixtures were heated using microwave irradiation, 100 °C, 5 min (100 W).

[b] Conversions determined by ^1H NMR. [c] 9 mol% of additive was used.

2.2.3 Optimisation

Complete conversion to **230** was still observed on lowering the reaction temperature to 80 °C, however, reactivity decreased at temperatures below that point (Table 2). When the reduction of DMI was carried out at 80 °C over 5 minutes with one equivalent of NMO to $Mo(CO)_6$ a drop in conversion from >99% to 56% was observed (entry 4, Table 2). Lower catalyst loading also resulted in lower yields (a yield of 22% was observed with a catalyst loading of 2 mol%, no product was observed at 1 mol%). Poor reactivity was observed when $PhSiH_3$ was replaced with less reactive silanes. Ph_2SiH_2 gave a 3% conversion by ^1H NMR whilst Cl_3SiH, $Me(EtO)_2SiH$, PMHS and Et_3SiH did not react at all. It was also found that the reactivity was unaffected when the reaction was heated in an oil bath.

Table 2 Effect of temperature and reaction time on the reduction of DMI

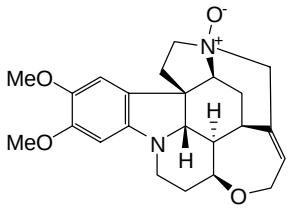


entry	temperature, °C	time, min	conversion, %[b]
1	100	5	100
2	80	10	100
3	80	5	>99 (95% yield)
4	80	5	56[c]
5	70	5	69
6	60	5	26
7	40	5	20

[a] Reaction conditions: DMI (1 equiv), $Mo(CO)_6$ (5 mol%), NMO (9 mol%), $PhSiH_3$ (1.5 equiv), THF (1 mL); reaction mixtures were heated using microwave irradiation, 5 min (100 W). [b] Conversions determined by ^1H NMR.

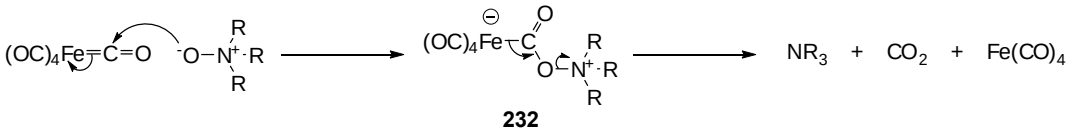
2.2.4 Oxidative Removal of Ligands from Metal Carbonyls

It was Hieber and Lipp who first reported the use of pyridine *N*-oxides to oxidatively remove carbonyl ligands from $Fe(CO)_5$.[61] In 1970 Alper and Edward illustrated the generality of this process by the deoxygenation of aliphatic, aromatic and heterocyclic amine *N*-oxides with $Fe(CO)_5$; this method of oxidative removal of carbonyl ligands was even carried out with brucine *N*-oxide (BNO) hydrate **231** (Figure 1).[62] Alper and Edward were the first to propose a mechanism for the transformation, a mechanism which is still widely accepted. Nucleophilic attack by the oxygen of the amine *N*-oxide on the carbonyl carbon occurs to form **232** which then eliminates the deoxygenated amine and carbon dioxide (Scheme 74).



231 : brucine *N*-oxide

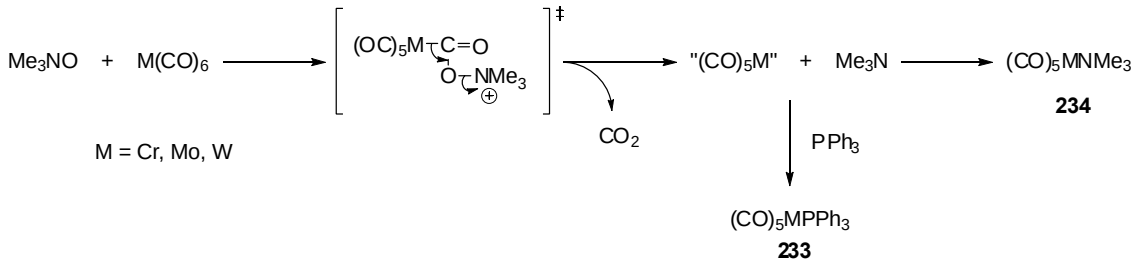
Figure 1 Brucine *N*-oxide



232

Scheme 74 Alper and Edward's mechanism for the decarboxylation of $Fe(CO)_5$ with amine *N*- oxides

With the use of amine *N*-oxides as oxidative decarboxylating reagents established,[63,64] Shi *et al*. carried out the first kinetic and mechanistic study into the reaction of trimethylamine *N*-oxide (TMANO) with the group 6 hexacarbonyls.[65] Shi *et al*. showed that carbon-oxygen bond making and metal-carbon bond breaking contributed to the energies of the rate determining step. After decarboxylation by TMANO, $(CO)_5MPPh_3$ (M = Cr, Mo, W) was formed in the presence of PPh_3 and $(CO)_5MNMe_3$ in the absence of phosphine (Scheme 75).



234

233

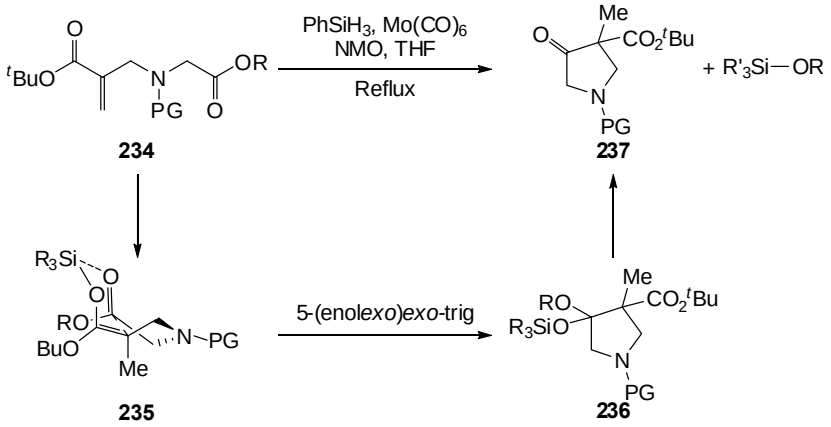
Scheme 75 Oxidative decarboxylation of $M(CO)_6$ (M = Cr, Mo, W)

The use of amine *N*-oxides in transition metal catalysed organic transformations has been dominated by the Pauson-Khand reaction (PKR) following the discovery of the accelerating effects amine *N*-oxides have on this reaction. Amine *N*-oxides allow PKRs to be carried out at room temperature in high to excellent yields.[66,67] More recent developments have seen the introduction of recyclable amine *N*-oxides bound to a solid phase[68] and also the use of

chiral amine *N*-oxides in asymmetric PKRs by desymmetrisation of cobalt-alkyne complexes.[69-75]

2.3 Molybdenum-Catalysed Reductive Dieckmann Condensation

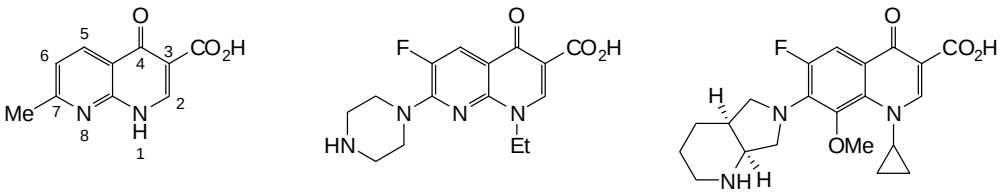
Following work by Frost *et al*. on the Michael Dieckmann condensation forming 3,3'-disubstituted 4-oxopyrrolidines (*cf*. 2.1), we set out to develop a reductive Dieckmann condensation using molybdenum catalysis. Scheme 76 shows the envisaged reductive Dieckmann condensation, hydrosilylation of **234** would give silyl ketene acetal **235** which would undergo a 5-(enol*exo*)*exo*-trig cyclisation, this is formally favoured by Baldwin's rules.[76] Siloxane elimination gives 3,3'-disubstituted 4-oxopyrrolidine **237**, a useful intermediate in the synthesis of fluoroquinolone antibacterials and their analogues.



Scheme 76 Envisaged molybdenum-catalysed reductive Dieckmann condensation

2.3.1 Fluoroquinolones

Fluoroquinolones are a potent class of antibacterial agents with a broad spectrum of activity making them a valuable target in synthesis.[77] Following the discovery of Nalidixic acid **238** (a by-product from the synthesis of chloroquinine), structure-activity relationship studies soon showed that quinolones fluorinated at the C-6 position with a nitrogen containing heterocycle at the C-7 position showed fewer toxic effects, improved pharmacokinetic properties and extensive and potent activity against Gram-positive and Gram-negative bacteria (Figure 2).



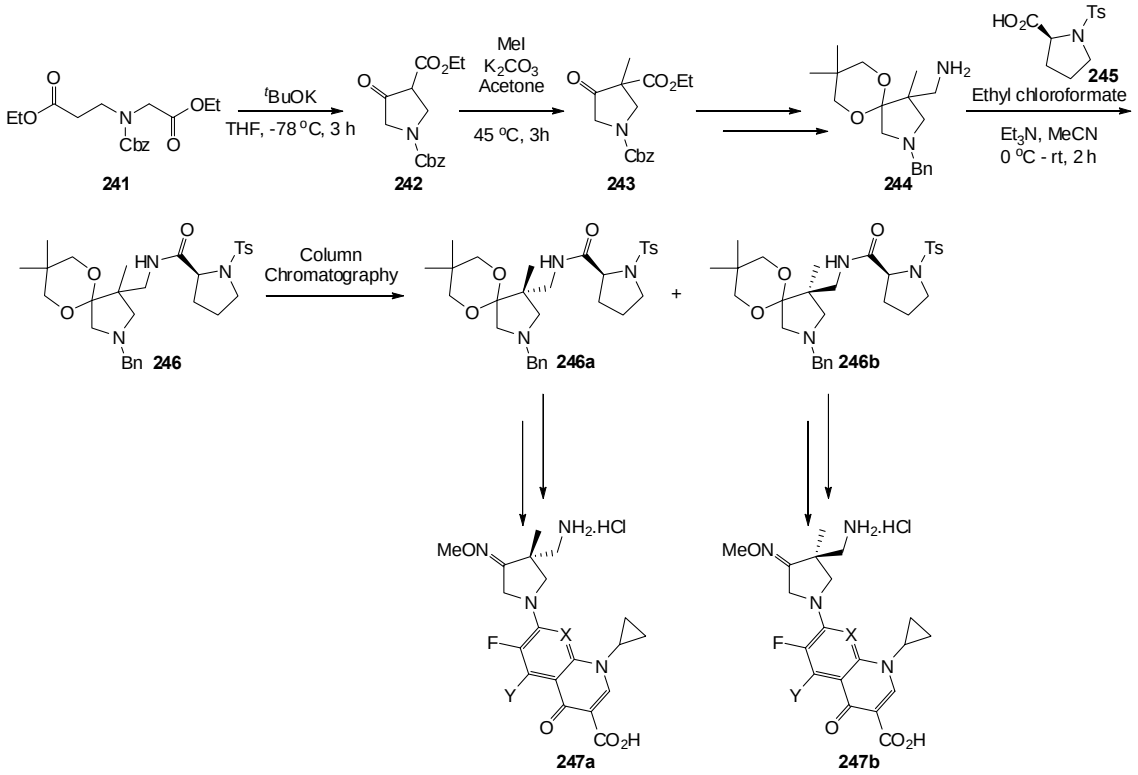
238 : Nalidixic acid
FDA approved 1963

239 : Norfloxacin
FDA approved 1986

240 : Moxifloxacin
FDA approved 1999

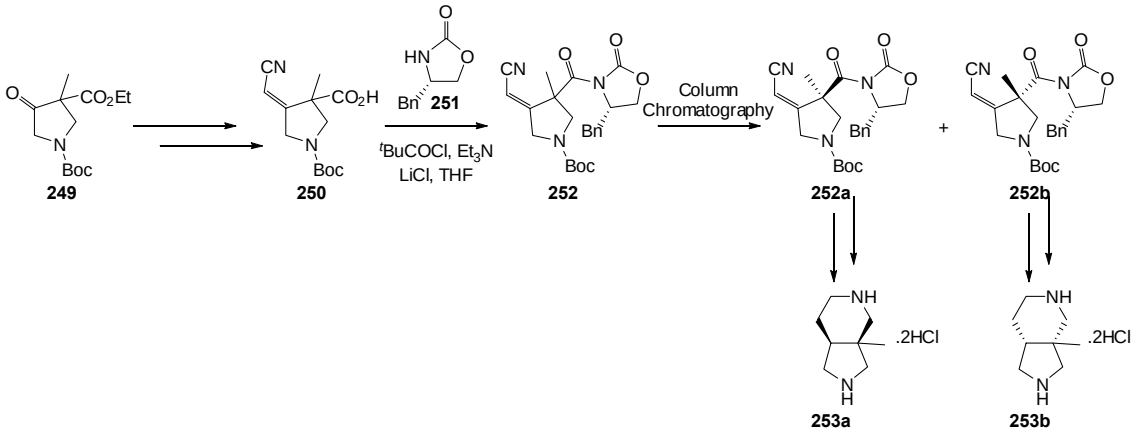
Figure 2 Fluoroquinolone antibacterials

In 2004, Choi *et al*. synthesised fluoroquinolones **247a** and **247b** containing a chiral oxiimino pyrrolidine at the C-7 position. These new fluoroquinolones showed excellent *in vitro* antibacterial activities and pharmacokinetic profiles.[78] *N*-Carboxybenzyl protected 3,3'-disubstituted 4-oxopyrrolidine **243** was prepared by the Dieckmann condensation of glycine derived **241**, followed by alkylation by methyl iodine.[79] Optically-enriched products were obtained by resolution: *N*-tosyl protected L-proline was attached to the primary amine of **244** and diastereomers **246a** and **246b** were separated by column chromatography. This was followed by the base-catalysed removal of the amino acid (Scheme 77).



Scheme 77 Choi's synthesis of fluoroquinolone antibacterials **247a** and **247b**

Kim *et al*. synthesised analogues of the pyrrolopiperidine side group of Moxifloxacin **240**.[80] Again, access to optically-enriched materials was achieved by the separation of diastereomers **252a** and **252b** by column chromatography and subsequent removal of the optically active oxazolidinone **251** (Scheme 78).

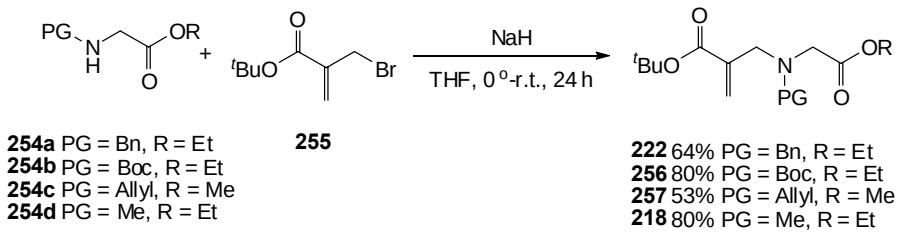


Scheme 78 Synthesis of 3a-methylpyrrolo[3,4-*c*]piperidine

Although effective, resolution of products obtained from racemic 3,3'-disubstituted 4-oxopyrrolidines **243** and **249** does result in poor atom and step economy. We envisage that, through an asymmetric reductive Dieckmann condensation, optically active 3,3'-disubstituted 4-oxopyrrolidines could be obtained efficiently from α-substituted acrylic esters.

2.3.2 Racemic Molybdenum-Catalysed Reductive Dieckmann Condensation

To study the molybdenum-catalysed reductive Dieckmann condensation, a range of α-substituted acrylate esters was synthesised bearing different nitrogen functionalities. Using a synthetic route developed by Greaney *et al*.,[81] substrates were formed by the alkylation of the corresponding *N*-protected glycine ethyl or methyl ester with *tert*-butyl 2-(bromomethyl)acrylate; **218** was formed from the alkylation of sarcosine ethyl ester (Scheme 79).[4,81]



254a PG = Bn, R = Et
254b PG = Boc, R = Et
254c PG = Allyl, R = Me
254d PG = Me, R = Et

255

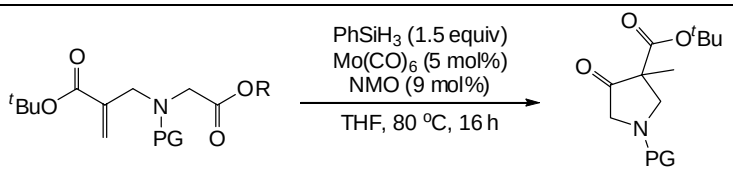
222 64% PG = Bn, R = Et
256 80% PG = Boc, R = Et
257 53% PG = Allyl, R = Me
218 80% PG = Me, R = Et

Scheme 79 Substrate synthesis

Extended reaction times were required to allow for cyclisation to the desired product (Table 3, entries 1-3). Even with shorter reaction times, acrylate **222** was completely consumed, the corresponding uncyclised, conjugate reduction product was the only other product observed with reaction times of four and eight hours (Table 3, entries 1 and 2). Benzyl substitution on the nitrogen atom gave the most favourable yield with 3,3'-disubstituted 4-oxopyrrolidine **258** being isolated in an 88% yield (Table 3, entry 3). A lower yield was observed with the electron-withdrawing Boc substitution (entry 3) while a number of side products were observed in the reductive Dieckmann condensation of allyl substituted **259**

(entry 5). A low yield was also observed for the formation of methyl substituted **260** (entry 6).

Table 3 Molybdenum-catalysed reductive Dieckmann Condensation

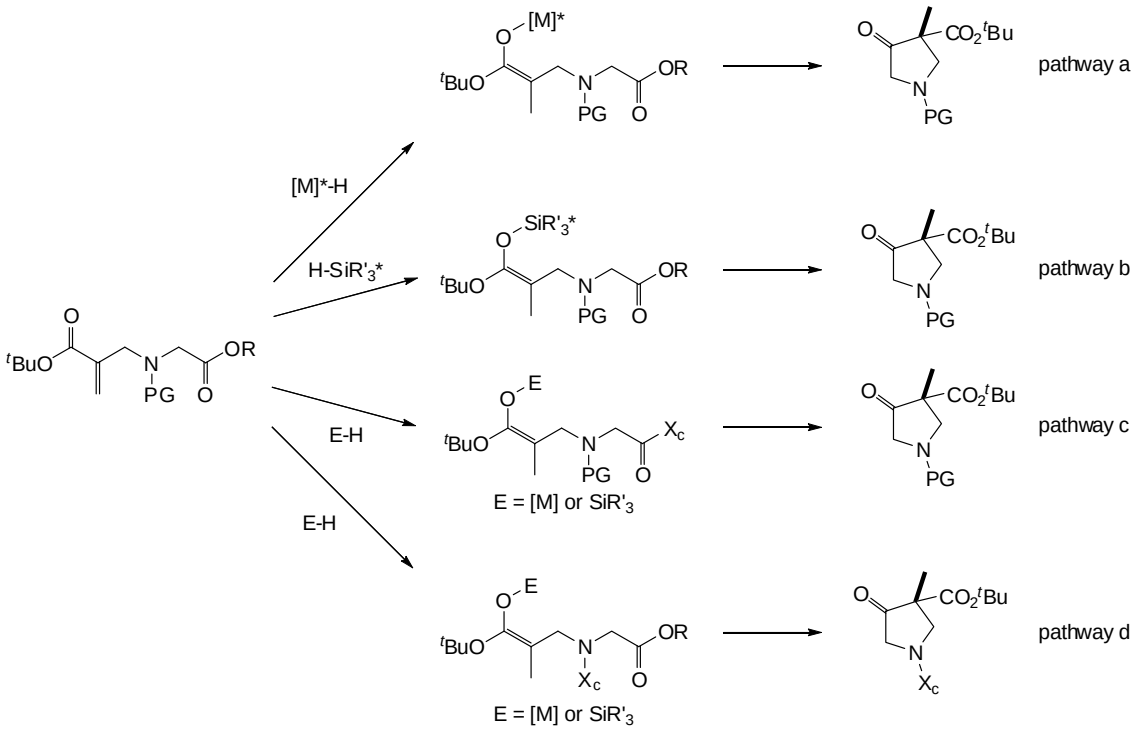


entry	protecting group	R	time, h	product	yield, %[b]
1	Benzyl	Et	4	**258**	57
2	Benzyl	Et	8	**258**	74
3	Benzyl	Et	16	**258**	88
4	Boc	Et	16	**249**	61
5	Allyl	Me	16	**259**	51
6	Methyl	Et	16	**260**	67

[a] Reaction conditions : Substrate (1 equiv), $PhSiH_3$ (1.5 equiv), $Mo(CO)_6$ (5 mol%), NMO (9 mol%), THF, reflux, 16 h. [b] Isolated yields.

2.3.3 Asymmetric Reductive Dieckmann Condensation

Having established precedent for the reductive Dieckmann condensation, attention was focused on asymmetric induction at the newly formed quaternary centre. A number of pathways were envisaged to form enantiomerically enriched products (Scheme 80). Firstly, ligation of the transition metal catalyst with a chiral ligand (pathway a), secondly, the formation of a chiral silyl ketene acetal (pathway b), and thirdly, the use of chiral auxiliaries either on the terminal ester (pathway c) or as a chiral amine protecting group (pathway d) were all envisaged.



Scheme 80 Possible pathways to an asymmetric reductive Dieckmann condensation

2.3.3.1 Ligation of Molybdenum

A large amount of research has been focused on the molybdenum-catalysed asymmetric allylic alkylation reaction.[25] High enantioselectivities were achieved by the use of nitrogen donor ligands such as pyridylamides **261**, bis(dihydrooxazoles) **262** and bipyridines **263** (Figure 3). Unfortunately, there have been no reports of a molybdenum-catalysed asymmetric conjugate reduction. It was envisaged that a chiral molybdenum-hydride species could be accessed on addition of phenylsilane to a molybdenum complex containing chiral *N*-donor ligands.

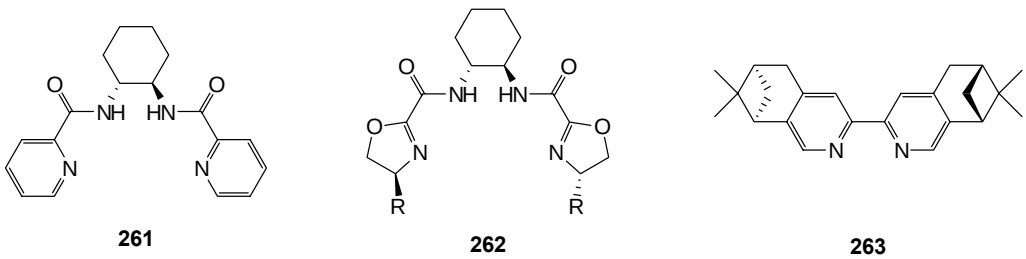
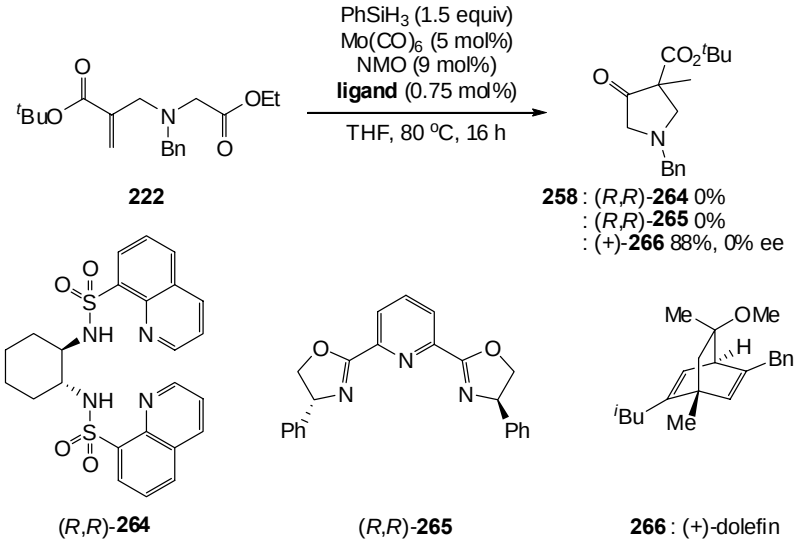


Figure 3 Common ligands for molybdenum-catalysed asymmetric allylic alkylations

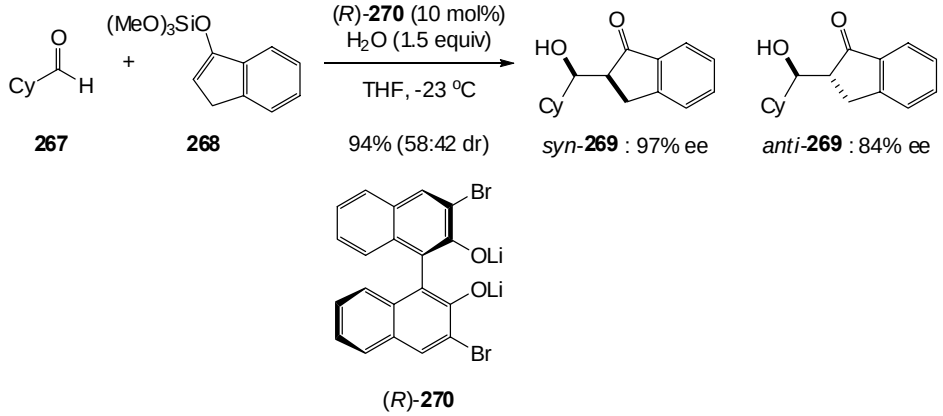
Ligands **264** and **265** (Scheme 81), 1.5 equivalents to molybdenum, were added to a solution of $Mo(CO)_6$ and NMO in THF and stirred for an hour at 80 ^oC, in both instances a deep red solution was observed. After addition of all other reagents, and a further 16 hours heating, only starting material was observed. Following on from these results, chiral diene **266** was used (1.5 equivalents to molybdenum) giving the desired product in 88% isolated yield as the racemate (Scheme 81). This suggests that either the ligand is not interacting with the metal centre or that it is a silicon, not a molybdenum, enolate which attacks the terminal ester. In light of these results no further attempts were made to induce chirality by ligation of molybdenum.



Scheme 81 Asymmetric molybdenum-catalysed reductive Dieckmann condensation using chiral ligands

2.3.3.2 Ligation of Silicon

Extensive research has been carried out into the use of chiral Lewis acids in organosilcon chemistry which enables the formation of chiral, hypervalent silicon species (the chemistry of hypervalent silicon will be discussed in Chapter 4).[82,83] In one example from Nakajima *et al*., lithium binaphtholate **270** enabled an asymmetric Mukaiyama aldol reaction forming *syn*-**269** in 97% ee and *anti*-**269** in 84% ee (Scheme 82).[84]

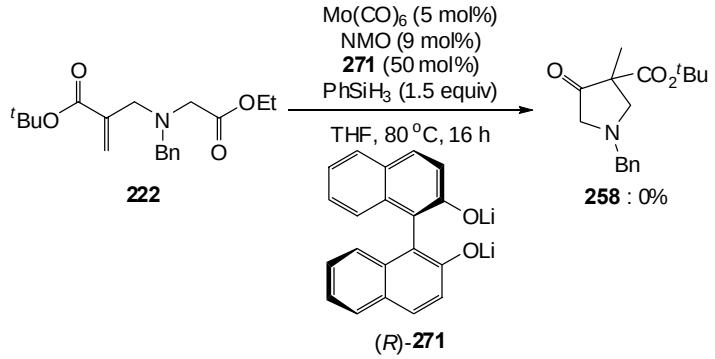


267 **268** 94% (58:42 dr) *syn*-**269** : 97% ee *anti*-**269** : 84% ee

(*R*)-**270**

Scheme 82 Lithium binaphthol-catalysed asymmetric Mukaiyama aldol reaction

Assuming that the molybdenum reductive Dieckmann condensation proceeds *via* a silyl ketene acetal, it was proposed that the introduction of a chiral Lewis base would result in a chiral silyl ketene acetal and in turn an enantiomerically enriched product. 50 mol% of $[Li_2\{(R)\text{-binol}\}]$[85] **271** was added to the reaction mixture which was refluxed for 16 hours. Crude ^{1}H NMR and TLC analysis showed the formation of a multitude of compounds from which no products were isolated.



222 **258** : 0%

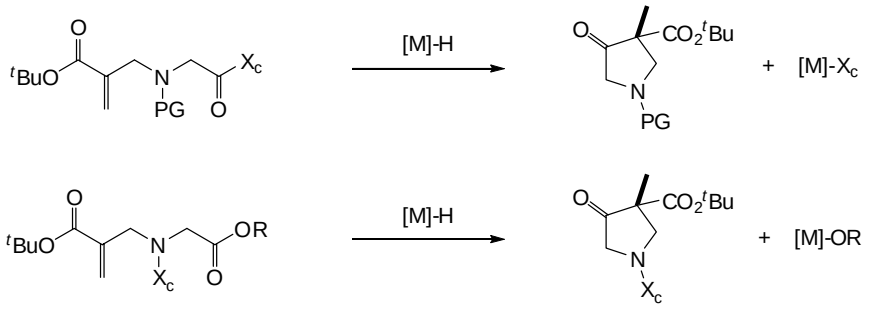
(*R*)-**271**

Scheme 83 Lithium binaphthol-directed reductive Dieckmann condensation

2.3.3.3 Chiral Auxiliaries

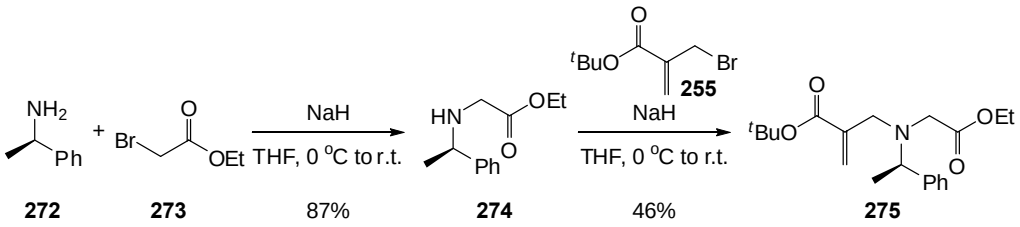
Although criticised for poor step economy and cost of stoichiometric amounts of auxiliary, the introduction of chirality by the use of chiral auxiliaries still remains a powerful tool in asymmetric organic synthesis.[86] An enantioselective version of this reductive Dieckmann condensation could be envisioned by using a chiral auxiliary either on the terminal ester

moiety or on the nitrogen atom (Scheme 84). Attachment of the chiral auxiliary to the terminal ester offers a particularly attractive approach as the directing group would be acting as a traceless chiral auxiliary and could be recovered from the reaction mixture, reducing process cost.



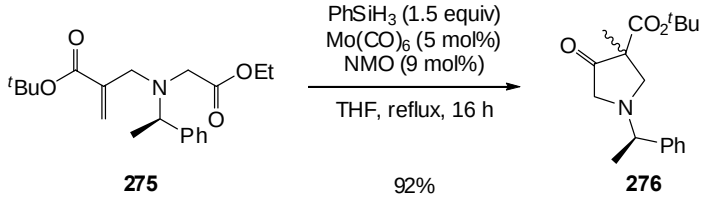
Scheme 84 Chiral auxiliary directed asymmetric reduction Dieckmann condensation

To investigate the effect of a chiral nitrogen substitutent, α-substituted acrylic ester **275** was synthesised using inexpensive, readily available (*R*)-α-methylbenzylamine. Alkylation of (*R*)-α-methylbenzylamine **272** by ethyl bromoacetate **273** proceeded smoothly to give **274** in 87% yield, which was alkylated by **255** to give **275** in 46% yield (Scheme 85).



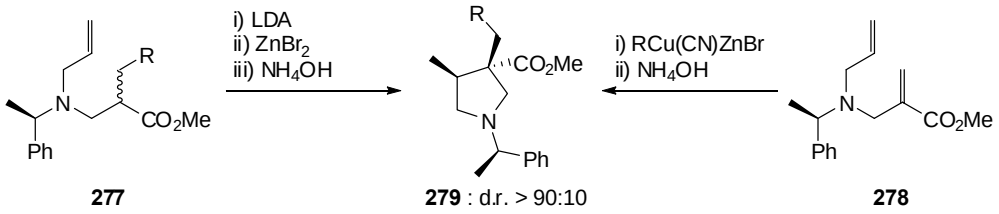
Scheme 85 Synthesis of **275**

275 was exposed to the molybdenum-catalysed reductive conditions described above (*cf.* 2.3.2) giving 3,3'-disubstituted 4-oxopyrrolidine **276** in 92% isolated yield. ^{1}H NMR analysis of **276** showed a 1:1 ratio of diastereomers, suggesting that the α-methylbenzylamino group is too removed from the reaction centre to induce any chirality (Scheme 86).



Scheme 86 Reductive Dieckmann condensation of chiral acrylic ester **275**

In a related example from Chemla *et al*., a chiral α-methylbenzylamino group was used to deliver high levels of diastereoselectivity for the synthesis of 3,4-disubstituted β-prolines *via* either a carbometalation or domino Michael addition/carbometalation reaction (Scheme 87).[87] The high levels of control are a consequence of zinc(II)-Ar interactions as well as zinc(II) interactions with the carbomethoxy and nitrogen mioeties. It is the steric interaction between the methyl and allyl moieties in **281** which makes it less favourable than **280** (Figure 4).



Scheme 87 Diasterocontrolled synthesis of enantioenriched 3,4-disubstituted β-prolines

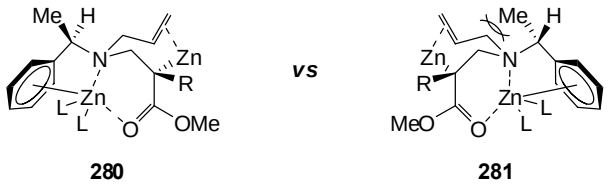
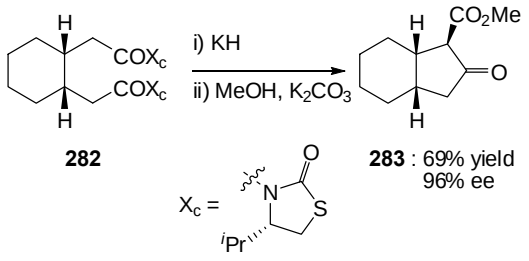


Figure 4 Origin of the chirality transfer in the carbocyclisation reaction from zinc enolates

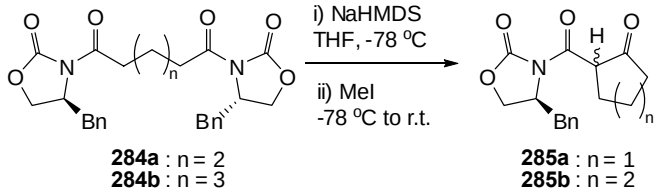
In light of the disappointing asymmetric results we next turned to the use of a traceless chiral auxiliary as the terminal ester moiety.

Nagao *et al*. used traceless chiral auxiliaries in a Dieckmann condensation giving the annulation product in excellent enantiomeric excess.[88] Diamide **282** was cyclised under basic conditions and, following methanolysis, gave methyl ester **283** in 69% overall yield and 96% ee (Scheme 88).



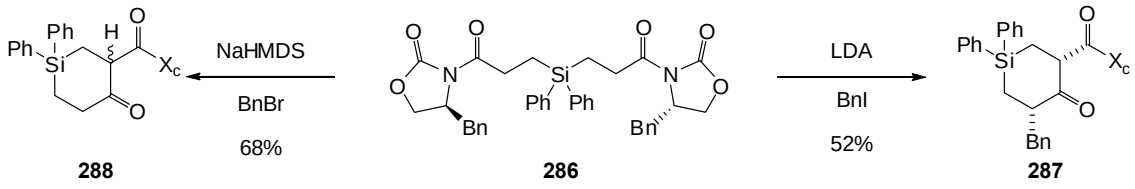
Scheme 88 Asymmetric Dieckmann condensation directed by 4(*S*)-isopropyl-1,3-thiazolidine-2-thione

Later, Trova and Wang, whilst attempting the asymmetric double alkylation of **284a** and **284b**, observed Dieckmann products **285a** and **285b** respectively.[89] Moderate yields (55% for both **285a** and **285b**) were observed and the two diastereomers of **285a** were isolated in a 1:1 ratio (Scheme 89).



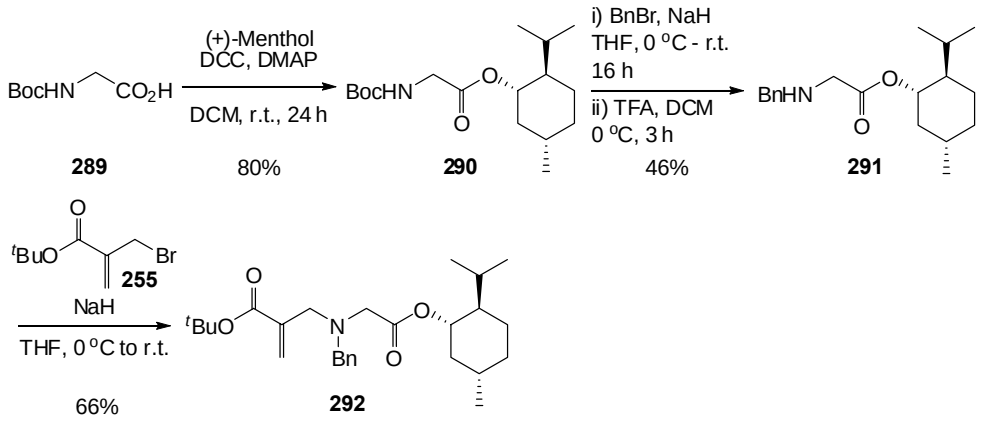
Scheme 89 Dieckmann condensation directed by oxazolidinones

Sieburth and Chen found that a tandem alkylative Dieckmann reaction of organosilane **286** could be achieved using LDA, giving alkylative Dieckmann product **287** as the *syn*-product. It was found that on switching to NaHMDS, like Trova and Wang, only Dieckmann condensation product **288** was observed (Scheme 90).[90]



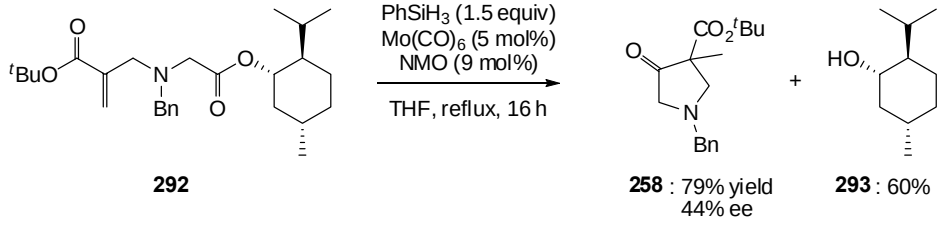
Scheme 90 Alkylative Dieckmann Condensation

Due to its relatively low cost and availability, initial studies into the effect of a chiral terminal ester moiety focused on (+)-menthol ester **292**. *N*-Boc glycine menthol ester **290** was synthesised as described by Franchini.[91] Benzylation of **290** and removal of the Boc protecting group gave *N*-benzyl glycine menthol ester **291**; this was alkylated by acrylic ester **255** to give substrate **292** (Scheme 91).



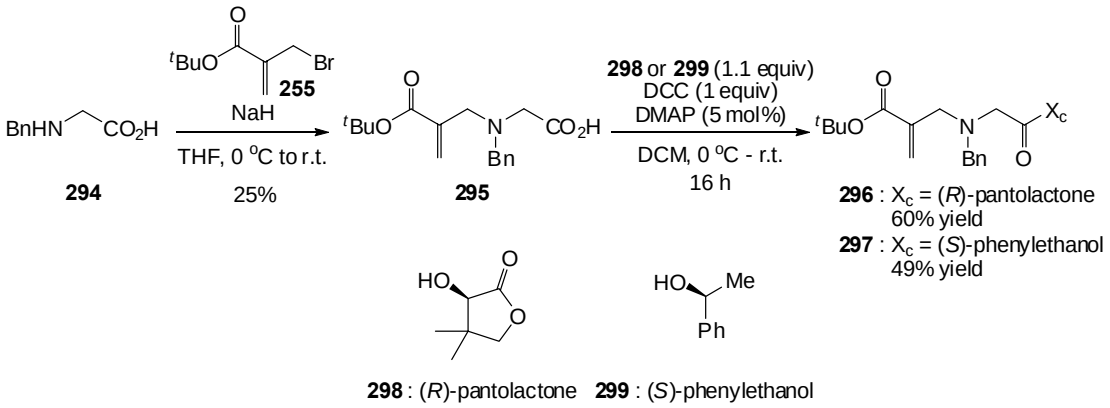
Scheme 91 Synthesis is (+)-menthol ester **292**

The reductive Dieckmann condensation of **292** using the conditions described above (*cf.* 2.3.2) proceeded smoothly forming **258** in 79% isolated yield with a 60% recovery of (+)-menthol **293** (Scheme 92). HPLC analysis of **258** showed a 44% ee for this transformation.



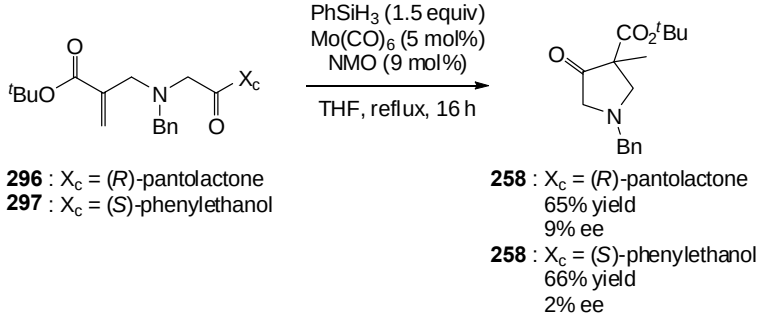
Scheme 92 Asymmetric reductive Dieckmann condensation of **292**

To investigate the effect of the chiral auxiliaries further, esters of (*R*)-pantolactone **298** and (*S*)-1-phenylethanol **299** were formed from the coupling with acid **295** and the required alcohol. Carboxylic acid **295** was accessed form the alkylation of *N*-benzyl glycine **294** by acrylate **255** (Scheme 93).



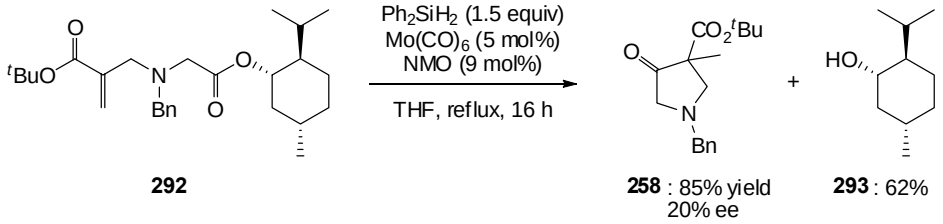
Scheme 93 Synthesis of chiral esters **296** and **297**

258 was formed from both **296** and **297** in comparable yields to that observed with the mentholate ester **292**, however, poor enantioselectivity was observed: 9% and 2% ee respectively (Scheme 94).



Scheme 94 Reductive Dieckmann condensation of **296** and **297**

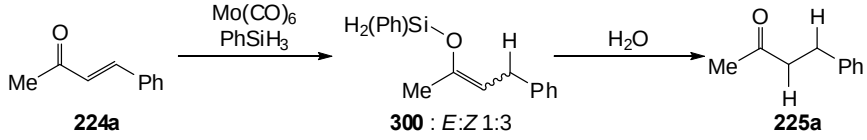
Using menthol ester **292**, a silane screen was carried out to see what effect the bulk of the silyl ketene acetal has on the enantioselectivity of the reaction. Knowing that PMHS, $(EtO)_2MeSiH$, Et_3SiH and Cl_3SiH do not reduce Michael acceptors under molybdenum catalysis (*cf.* 2.2.2),[5] Ph_2SiH_2 and Ph_3SiH were used. Like the other less reactive silanes, Ph_3SiH gave no product, while Ph_2SiH_2 gave reductive Dieckmann product **258** in 85% isolated yield (Scheme 95). A decrease in enantioselectivity was observed, 20% ee, despite the increased bulk of the silane. It is likely that the decrease in enantioselectivity is a consequence of the increased Lewis acidity of the silicon centre formed after hydrosilylation of **292**; this electronic effect is likely to increase the rate of cyclisation.



Scheme 95 Asymmetric molybdenum-catalysed reductive Dieckmann condensation with Ph_2SiH_2

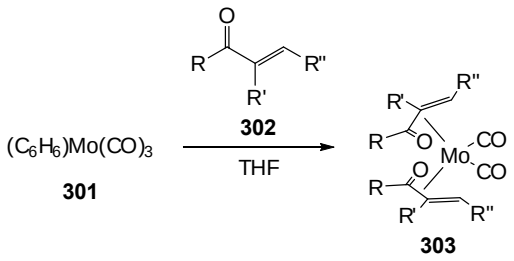
2.3.4 Proposed Mechanism

In the initial report of the molybdenum-catalysed conjugate reduction using phenylsilane, Keinan *et al*. showed that the reaction proceeds *via* a silyl enol ether with a hydride delivered from the silane to the β-carbon and a proton delivered to the α-carbon on hydrolysis (Scheme 96).[5] Unfortunately, no further mechanistic evidence was gathered from this study and the exact role of any molybdenum species formed in this process remains unclear.



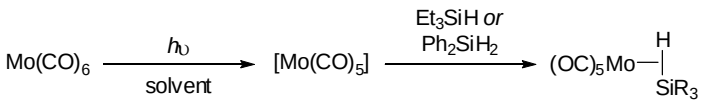
Scheme 96 Keinan's mechanistic insight

Another observation from Keinan is that Michael acceptors with fixed transoid conformation were not reduced under these conditions, suggesting that an η^4-1-oxa-1,3-diene molybdenum species are formed with the coordinatively unsaturated molybdenum acting as a Lewis acid activator of the Michael acceptor. The formation, isolation and catalytic activity of a number of molybdenum oxadiene complexes **303** were explored by Schmidt (Scheme 97).[92,93]



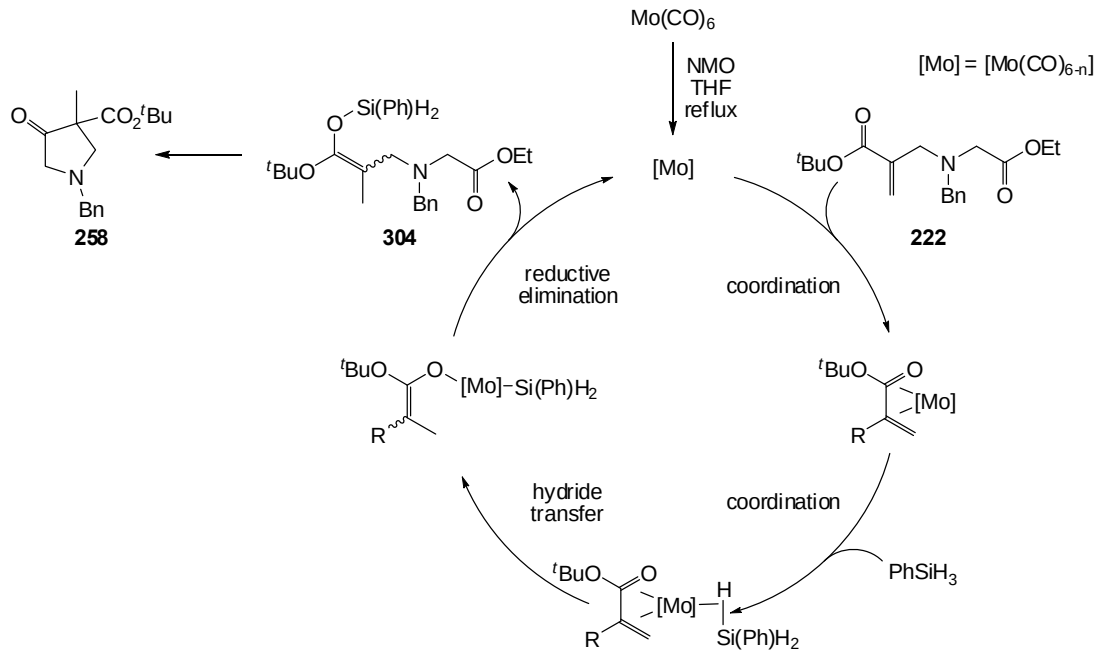
Scheme 97 Schmidt's synthesis of oxadiene molybdenum species

The η^2-coordination of a silicon-hydrogen bond to a metal centre has significant consequences for the activity of the Si-H bond in transition metal catalysed hydrosilylations.[94] Activation of Si-H bonds by η^2-coordination to molybdenum has been observed for primary, secondary and tertiary silanes, with Si-H bond elongation being observed.[95-100] These σ-complexes are often formed by either thermally or photochemical decarboxyation of $Mo(CO)_6$ to give $[Mo(CO)_5]$ which reacts with the silane (Scheme 98).



Scheme 98 Synthesis of η^2-$HSiR_3$ complexes of $Mo(CO)_6$

With no evidence of a molybdenum-hydride species being formed form oxidative insertion into a Si-H bond we propose a mechanism in which the molybdenum is coordinated, and therefore activating, both the Michael acceptor and the silane (Scheme 99). Delivery of the hydride to the β-carbon of the Michael acceptor is followed by reductive elimination giving silyl ketene acetal **304** which undergoes an 5-(enol*exo*)*exo*-trig cyclisation to give 3,3'-disubstituted 4-oxopyrrolidine **258**.



Scheme 99 Catalytic cycle for the molybdenum-catalysed conjugate reduction of Michael acceptors

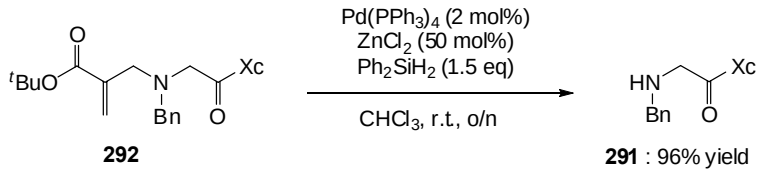
2.4 Exploring Other Metal Catalysts

Taking 44% ee as the highest achievable selectivity under molybdenum catalysis we looked to other transition metals to catalyse this transformation. The conjugate reduction literature is dominated by the late group transition metals ruthenium, cobalt, rhodium, iridium, nickel, palladium and copper as well as indium.[101] Using menthol ester **292**, we screened a range of catalysts which resulted in the isolation of a number of products.

2.4.1 Indium- and Palladium-Catalysed Reductive Dieckmann Condensation

Both indium- and palladium reductive conditions failed to give the desired reductive Dieckmann product. For indium-catalysis, reductive conditions described by Miura and Hosomi were adapted for this reductive process using $In(acac)_3$ and $In(OAc)_3$ as catalysts and $PhSiH_3$ as the stoichiometric reductant.[102] Only starting material was recovered after the reaction was stirred in THF at 80 ^{o}C for 24 h.

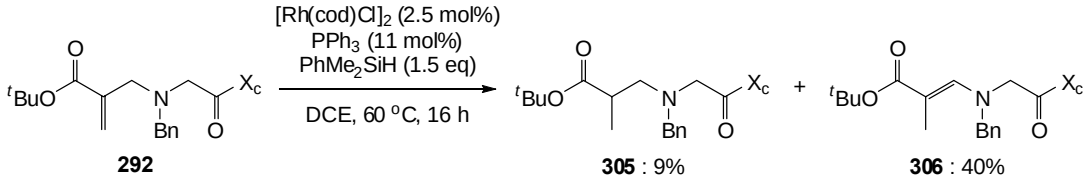
Complete consumption of **292** was observed using palladium, however, under these conditions from Keinan and Greenspoon,[103] the only product observed was *N*-benzyl glycine menthol ester as a result of removal of the allyl unit from the amine linker (Scheme 100).[104]



Scheme 100 Palladium-catalysed allyl deprotection of **291**

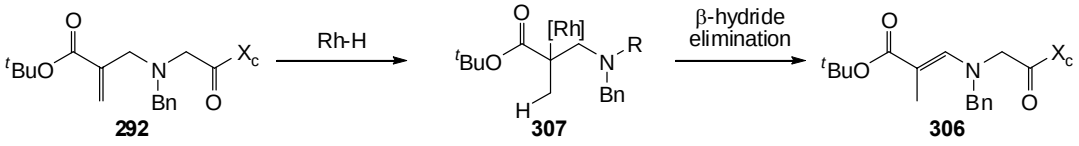
2.4.2 Rhodium-Catalysed Reductive Dieckmann Condensation

As with palladium and indium catalysis, reduction with rhodium did not yield the desired product. The rhodium-catalysed reduction was undertaken using adapted conditions from Morken *et al*.,[105] using $[Rh(cod)Cl]_2$ ligated by PPh_3 with Me_2PhSiH as the stoichiometric reductant. The reaction gave isomerised product **306** in 40% yield and conjugate reduction product **305** in a 9% yield (Scheme 101).

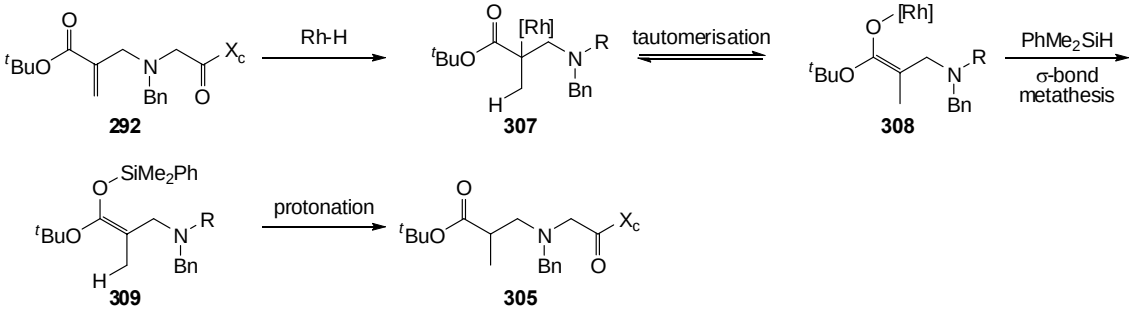


Scheme 101 Rhodium-catalysed reduction of **292**

It is proposed that hydrorhodiation of **292** gives organorhodium species **307** and β-hydride elimination results in the formation of enamine **306** (Scheme 102).[106] Tautomerisation of **307** to rhodium enolate **308**, occurring at a slower rate than β-hydride elimination, is followed by σ-bond metathesis to give silyl ketene acetal **309** which is protonated on work up to give conjugate reduction product **305** (Scheme 103).



Scheme 102 Rhodium-catalysed isomeration of **292**

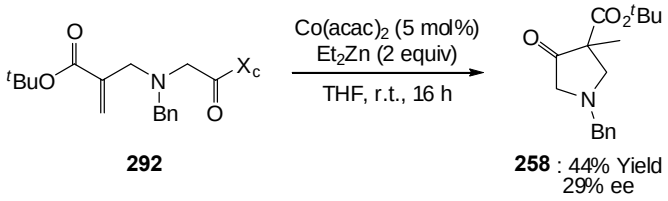


Scheme 103 Rhodium-catalysed conjugate reduction of **292**

2.4.3 Cobalt- and Nickel-Catalysed Reductive Dieckmann Condensation

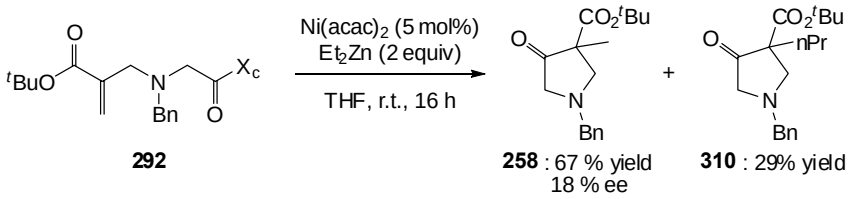
Lam *et al*. have developed both cobalt- and nickel-catalysed reductive aldol and reductive Mannich reactions which use Et_2Zn as a stoichiometric reductant.[107-113] The required cobalt- and nickel-hydride species are formed by the transmetallation of an ethyl group onto the cobalt or nickel centre which undergoes β-hydride elimination to give the metal hydride species and ethene.

Reduction of **292** under Lam's cobalt-catalysed reductive conditions[107] gave the desired reductive Dieckmann product **258** in a 44% isolated yield with a 51% recovery of **292**. Analysis of the product showed an enantioselectivity of 29% ee (Scheme 104).



Scheme 104 Colbalt-catalysed reductive Dieckmann condensation

Complete consumption of **292** was observed with the nickel-catalysed reductive Dieckmann condensation using Lam's conditions,[109] higher reactivity, relative to the analogous cobalt reductive system, was also observed by Lam. The desired compound was isolated in a 67% yield with an 18% ee; however, the reaction was complicated by the formation of a second product, this was found to be the alkylative Dieckmann product **310,** isolated in 29% yield (Scheme 105). This product was formed from the nickel-catalysed conjugate addition of an ethyl group followed by Dieckmann condensation, this observation is unsurprising as Lam *et al*. reported a competitive alkylative aldol cyclisation when forming both γ-lactams and γ-lactones.[109]



Scheme 105 Nickel-catalysed reductive and alkylative Dieckmann condensation

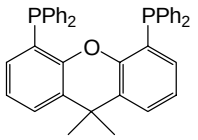
With the complication of the nickel-catalysed reductive Dieckmann condensation by the competitive alkylative Dieckmann condensation and with little scope to improve the disappointing selectivities, cobalt and nickel catalysis were pursued no further.

2.4.4 Copper-Catalysed Reductive Dieckmann Condensation

Copper hydride species, CuH, stabilised by phosphine ligands, are excellent catalysts for conjugate reduction and the chemistry of these species has been covered in recent reviews.[114,115] The use of copper as a catalyst for conjugate reductions grew exponentially from the first application of the hexamer $[(Ph_3P)CuH]_6$, Stryker's reagent.[116-119] Moving on from Stryker's reagent, a number of copper salts have been used for the *in situ* generation of CuH, including CuCl (with NaO^tBu as an additive), $(Ph_3P)CuF{\bullet}H_2O$, $Cu(OAc)_2$, $CuCl_2$, CuO^tBu and CuF_2. Predominantly, silanes have been employed as stoichiometric reductants, commonly the inexpensive polymethylhydrosiloxane, PMHS. Switching from triphenylphosphine to chiral bisphosphines leads to the generation of chiral CuH species capable of highly stereoselective 1,2- and 1,4-reductions. This is a very attractive

methodology due to the vast array of commercially available atropisomeric bisphosphines and ferrocenyl bisphosphines ligands.

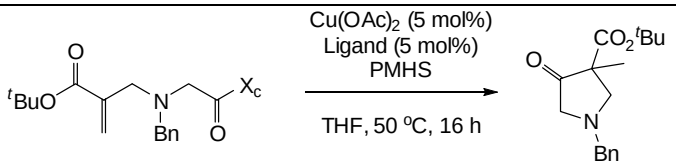
The initial investigation was into the effect of a range of achiral bisphosphines on the reductive Dieckmann condensation of **292**; $Cu(OAc)_2$ was employed as the precatalyst. Higher isolated yields and enantioselectivities were observed on using PMHS as the stoichiometric reductant compared to 1,1,3,3-tetramethylhydrosilane, TMDS (Table 4, entries 1-4). Moderate yields were observed for all ligands with the exception of dppf (entry 2), dppm (entry 5) and dppb (entry 8). The highest enantioselectivity was observed with dppe, 50% ee (entry 6); changes in the bite angle of the bisphosphine resulted in lower selectivity, particularly Xantphos **311** (Figure 5) whose tricyclic structure results in a notably large bite angle (entry 10). Changing from dppe to the more electron rich and bulkier dcpe resulted in a depletion of enantioselectivity whilst an increase in yield from 68% to 78% was observed (entry 9).



311 : Xantphos

Figure 5 Xantphos

Table 4 Ligand screen on achiral bisphosphine ligands



292 **258**

entry	ligand	yield (%)[b]	ee (%)[c]
1	dppf	5[d,e]	-
2	dppf	43	36
3	*rac*-BINAP	20[d]	41
4	*rac*-BINAP	59	48
5	dppm	21	44
6	dppe	68	50
7	dppp	73	46
8	dppb	20	43
9	dcpe	78	40
10	Xantphos	62	30

[a] Reaction conditions : **292** (0.2 mmol), PMHS (1.5 equiv), $Cu(OAc)_2$ (5 mol%), Ligand (5 mol%), THF, 50 °C, 16 h. [b] Isolated Yields. [c] Determined by HPLC (Chiracel OJ, 1% ^{i}PrOH : Hexane, 0.5 mL.min^{-1}). [d] TMDS (1.5 equiv) used in place of PMHS. [e] Conversion determined by ^{1}H NMR; product not isolated.

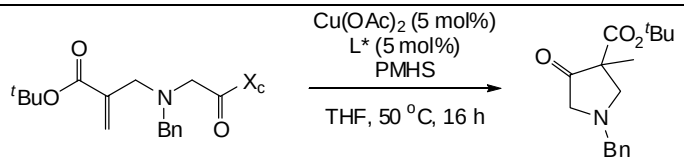
2.4.4.1 Effect of Chiral Ligands on Enantioselectivity

In light of the success of the copper-catalysed reductive Dieckmann condensation using achiral ligands, a range of chiral bisphosphines was screened for the reductive cyclisation of mentholate ester **292**.

An initial investigation into the match/mismatch effect between the two isomers of BINAP and the enantiomerically pure mentholate ester of **292** showed that, with esters of (+)-menthol, (*R*)-BINAP gave the highest selectivity with a 79% ee being observed against a selectivity of 14% being observed with (*S*)-BINAP (enties 1 and 2, Table 5). Following on from this study, the *R*-enantiomer of a range of chiral bisphosphines was screened (Table

5). Increasing the bulk of the aryl substituents on BINAP phosphines was found to deplete the selectivity of the reactions (entries 1, 3 and 4); a similar trend is observed with (*R*)-^{i}Pr-DuPhos **315** and (*R*)-Me-DuPhos **314** (entries 5 and 6). The use of ferrocene derived bisphosphines (*R*)-(*S*)- and (*S*)-(*R*)-Josiphos **316** gave **258** in excellent yields, however, poor enantioselectivities were observed in both cases (entries 7 and 8). Very poor selectivity was observed with (*R*)-PhanePhos **318** (entry 9) while moderate selectivity is observed with the BIPHEP derived (*R*)-SYNPHOS **317** (entry 10).

Table 5 Effect of chiral ligands of the copper-catalysed reductive Dieckmann condensation



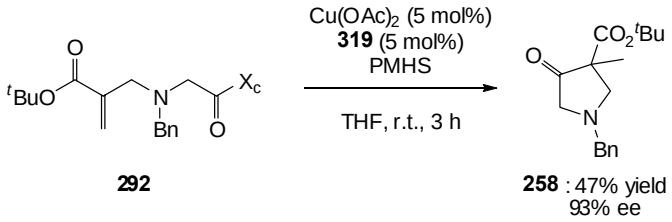
292 **258**

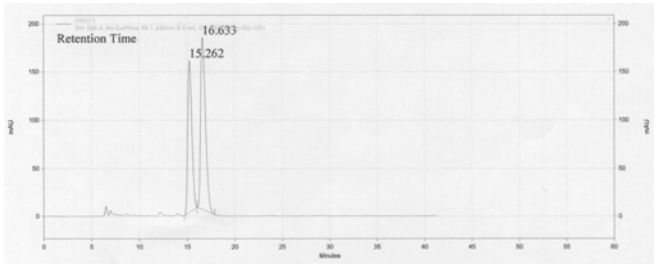
entry	ligand	yield (%)[b]	ee (%)[c]
1	(*R*)-BINAP	27	79
2	(*S*)-BINAP	62	14
3	(*R*)-Tol-BINAP	45	75
4	(*R*)-Xylyl-BINAP	79	35
5	(*R,R*)-^{i}Pr-DuPhos	66	46
6	(*R,R*)-Me-DuPhos	68	86
7	(*R*)-(*S*)-Josiphos	86	45
8	(*S*)-(*R*)-Josiphos	99	49
9	(*R*)-PhanePhos	53	15
10	(*R*)-SYNPHOS	52	65
11	(*R*)-P-Phos	78	63
12	(*R*)-Xylyl-P-Phos	58	91

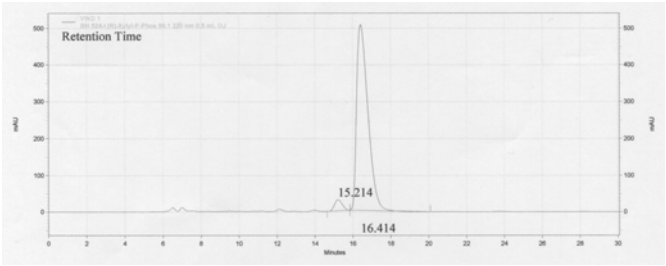
[a] Reaction conditions : **292** (0.2 mmol), PMHS (1.5 equiv), $Cu(OAc)_2$ (5 mol%), Ligand (5 mol%), THF, 50 °C, 16 h. [b] Isolated Yields. [c] Determined by HPLC (Chiracel OJ, 1% ^{i}PrOH : Hexane, 0.5 mL.min^{-1}).

With (*R*)-Me-DuPhos **314** appearing to be the ligand of choice, our attention turned to dipyridylphosphine ligand (*R*)-P-Phos **319** and its analogue (*R*)-Xylyl-P-Phos **320**. Developed by Chan *et al*., the P-Phos series of ligands has been used in the copper-catalysed asymmetric reduction of ketones with selectivities of up to 98% ee.[120-124] A

moderate enantioselectivity of 63% ee was observed with (*R*)-P-Phos (Table 5, entry 11), while (*R*)-Xylyl-P-Phos gave **258** in an excellent 91% ee with a decrease in yield being observed (entry 12). Carrying out the reaction at ambient temperature over 3 hours resulted in an increased selectivity, 93% ee, and a slight decrease in yield (Scheme 106).

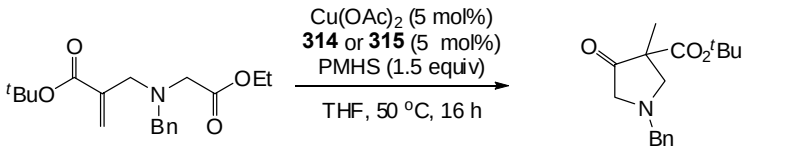






Scheme 106 Asymmetric copper-catalysed reductive Dieckmann condensation

The asymmetric copper-catalysed reductive Dieckmann condensation of **222**, with its terminal ethyl ester, was carried out using both (*R,R*)-Me-DuPhos **314** and (*R,R*)-^{i}Pr-DuPhos **315** as chiral ligands. Unlike the reductive cyclisation of mentholate ester **292**, (*R,R*)-^{i}Pr-DuPhos was found to give an enantiomeric excesses higher than that obtained with the use of (*R,R*)-Me-DuPhos: 20% ee and 15% ee, respectively (Scheme 107). These results clearly show the strong influence the (+)-menthol chiral auxiliary is having on this transformation, it is little wonder that enantiomeric excesses of up to 50% can be obtained with achiral bisphosphine ligands in conjunction with the chiral auxiliary.



222

258 : **314** 79% yield, 15% ee
315 26% yield, 20% ee

Scheme 107 Copper-catalysed asymmetric reductive Dieckmann condensation of **222**

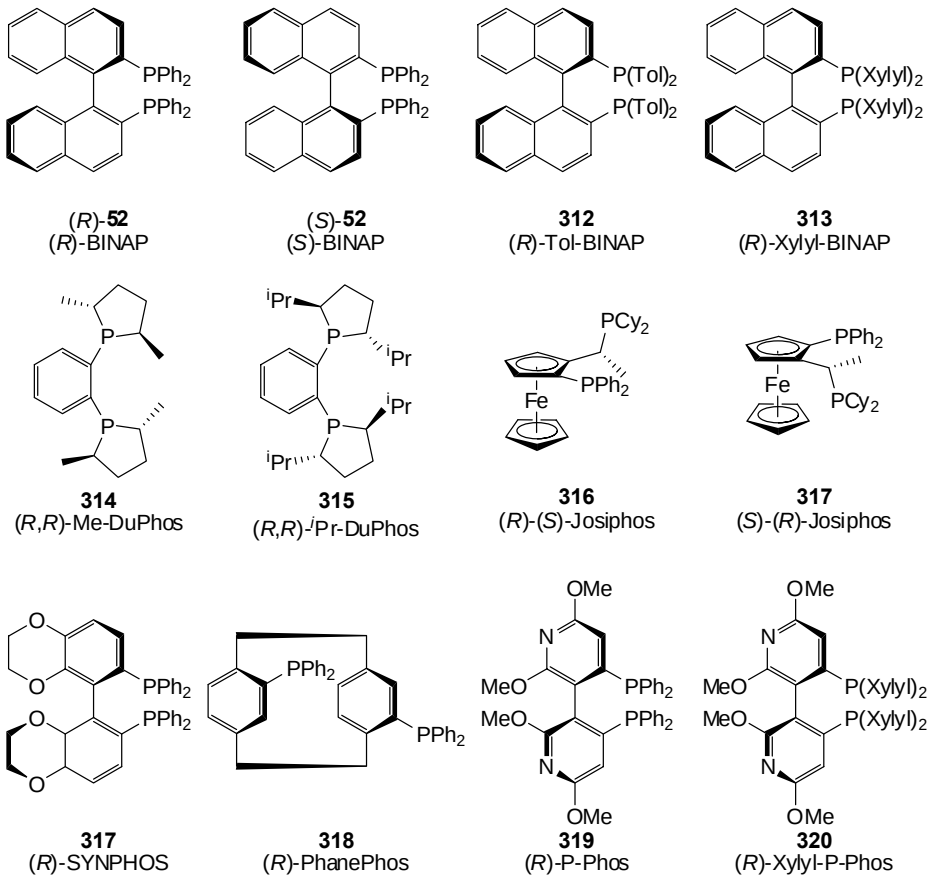
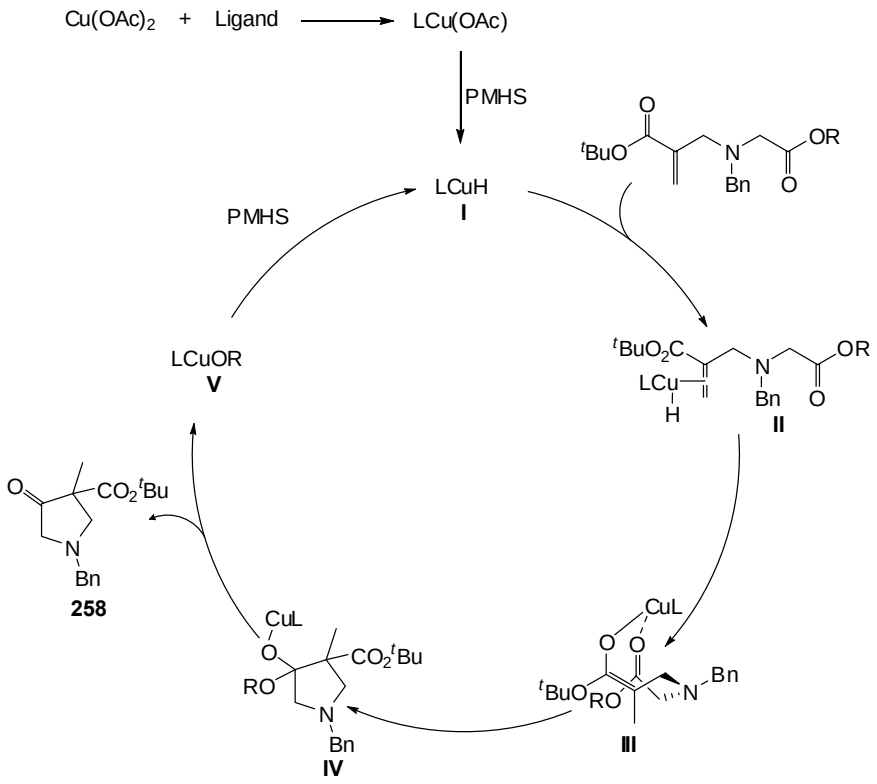


Figure 6 Chiral bisphosphines

2.4.4.2 Catalytic Cycle

Scheme 108 shows the proposed catalytic cycle for the copper-catalysed reductive Dieckmann condensation and is adapted from the catalytic cycles proposed for the copper-catalysed reductive aldol reaction.[114,115,125,126] *In situ* formation of CuH is followed by coordination of the copper centre to the Michael acceptor, forming π-complex **II**. The

copper enolate **III** is formed after delivery of hydride to the β-carbon atom. Lewis acid activation of the terminal ester and attack by the copper enolate onto the electrophilic centre occurs to give acetal **IV**. The acetal is then converted to the desired product **258** generating LCuOR **V**, an ideal precursor to LCuH which is rapidly reformed on reaction with PHMS.[114]

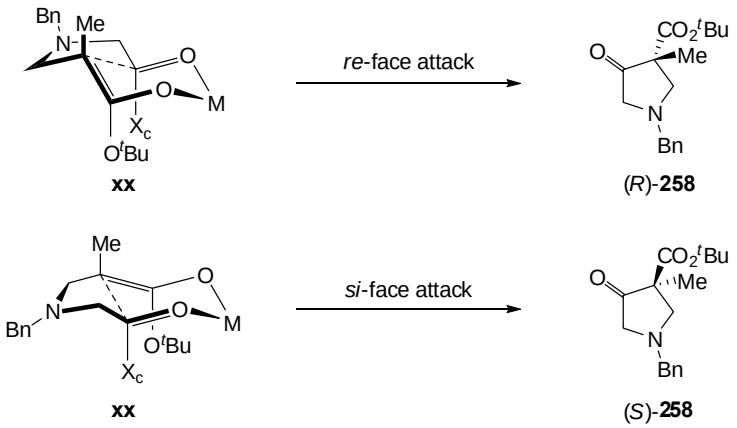


Scheme 108 Catalytic cycle for the copper-catalysed reductive Dieckmann condensation

2.4.4.3 Prediction of Absolute Stereochemistry

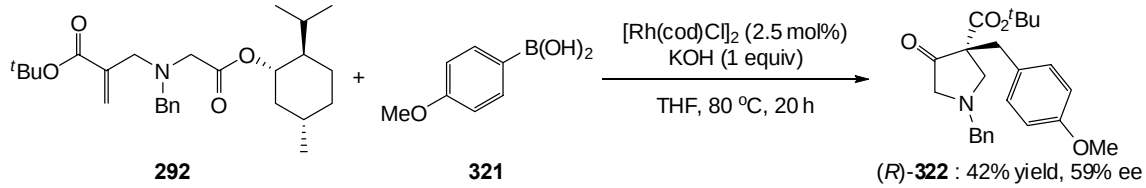
Unfortunately, attempts to determine the absolute stereochemistry of **258** by X-ray crystallography failed, as attempts to structurally modify **258** to give a crystalline derivative resulted in a multitude of products.

In the carbon-carbon bond forming step, attack of the enolate on *re*-face of the terminal ester and elimination of CuOR results in the formation of (*R*)-**258**, while attack on the *si*-face of the terminal ester results in the formation of (*S*)-**258** (Scheme 109).



Scheme 109 Enantioselectivity in the formation of **258**

In analogous, unpublished work, Frost *et al*. formed 3,3'-disubstituted 4-oxopyrrolindine (*R*)-**322** by the rhodium-catalysed Michael Dieckmann condensation of **292** (Scheme 110). This suggests that for the rhodium-catalysed Michael Dieckmann reaction, attack of the *si*-face of the mentholate ester is blocked by the isopropyl group of (+)-menthol.



Scheme 110 Rhodium-catalysed Michael Dieckmann condensation of mentholate ester **322**

2.5 Conclusion

A preliminary study has been carried out into the reductive Dieckmann condensation focusing on expeditious synthesis of enantiomerically enriched 3,3'-disubstituted 4-oxopyrrolidines containing an all-carbon quaternary centre.

Initial studies involved molybdenum-catalysis in which activation of the $Mo(CO)_6$ precatalyst occurred by the oxidative removal of carbonyl ligands by NMO. An enantiomeric excess of 44% was achieved when using (+)-menthol as a traceless auxiliary in this process.

$Cu(OAc)_2$ was identified as a suitable precatalyst for the same transformation. Enantiomeric excesses of up to 50% were observed with achiral bisphosphines, while enantiomeric excesses of up to 93% were recorded when (*R*)-Xylyl-P-Phos was used as a chiral bisphosphine ligand in conjunction with (+)-menthol as a chiral auxiliary.

As stated, this is a preliminary study, due to time constrains a full study into the reductive Dieckmann condensation was not carried out. Substrate scope is broad and a wide variety of chiral auxiliaries are available.

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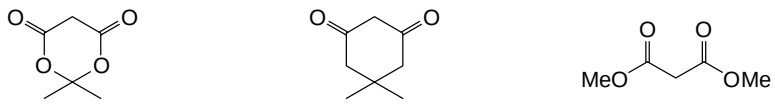
Chapter 3 - Two-Carbon Homologation of Aldehydes by Tandem Molybdenum-Catalysed Hydrosilylations

3.1 Meldrum's Acid and its Derivatives

Meldrum's acid **325** (MA) and its derivatives are important reagents in organic chemistry and have been used in the synthesis of a number of natural products and their analogues.[1] The range of chemistry carried out using MA has been covered in a number of reviews,[2-5] including one devoted to the synthetic applications of the pyrolysis of MA derivatives.[6] The unique reactivity of MA and its derivates comes as a consequence of MA's remarkable acidity (pK_a 7.3 in DMSO at 25 ^oC) compared to the related dimedone **326** and dimethylmalonate **327** (Figure 7),[7] a physical property owing to the fixed *E*-conformation of the two ester functionatities.[8-13]



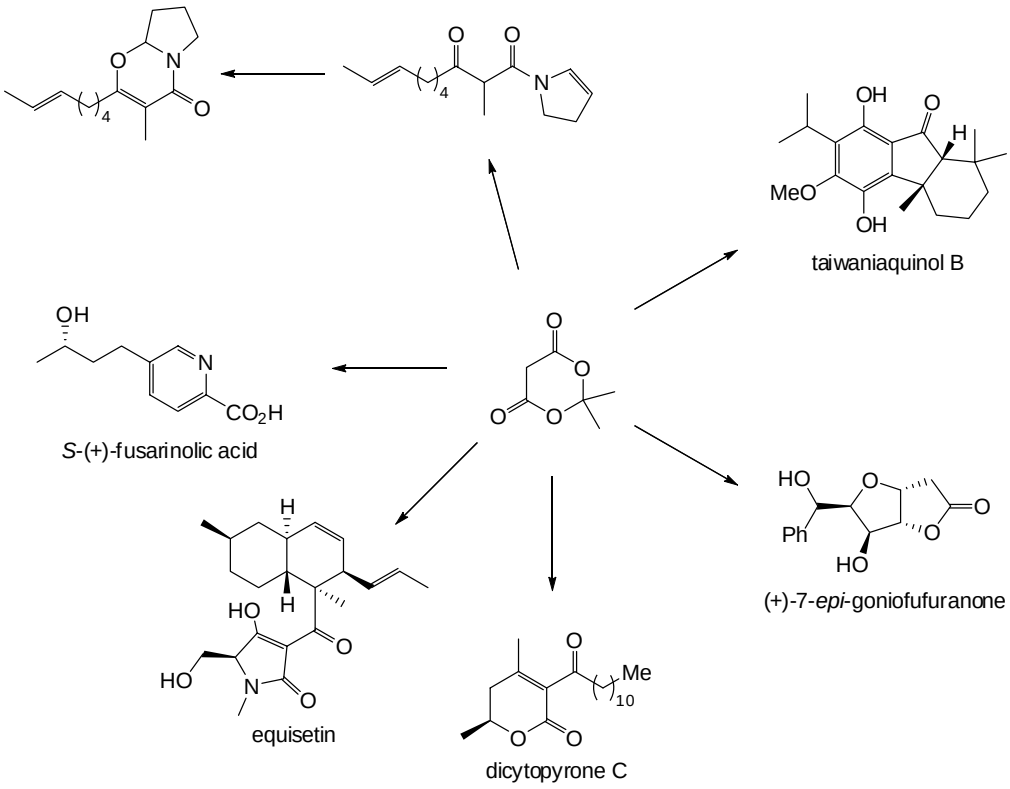
325
Meldrum's acid
pK_a : 7.3 (DMSO)

326
dimedone
pK_a : 11.2 (DMSO)

327
dimethyl malonate
pK_a : 15.9 (DMSO)

Figure 7 Comparable equilibrium acidities in DMSO solutions of MA, dimedone and dimethyl malonate

The synthesis of 1,3-dicarbonyl compounds from acyl malonates is one of the most important transformations carried out by MA derivatives. Nucleophilic attack at the one of the ester groups, often by an alcohol or amine, is followed by loss of acetone and carbon dioxide giving the 1,3-dicarbonyl compound which then can be carried through to a vast array of biologically active natural products and their analogues.[1] Beyond 1,3-dicarbonyl compounds, biologically active furanones, pyranones, tetramic acids and their analogues, terpeniods and pyridine alkaloids can be accessed from MA (Scheme 111).



Scheme 111 Examples of natural products synthesised from MA

3.1.1 Alkylidene Meldrum's Acid Derivatives as Michael Acceptors

Alkylidene MA derivatives, synthesised by the Knoevenagel condensation between aldehydes and MA, are of particular interest. Recently, Kaumanns and Mays demonstrated the high electophilicity of benzylidene MA derivatives by analysing the reaction kinetics of these derivatives with acceptor-substituted carbanions.[14] From this study, benzylidene MA **328a** was assigned an electrophilicity parameter comparable to that for carbocation **329** (Figure 8). The high electrophilicity of these substrates has been attributed to, like MA's high acidity, to the fixed *E*-conformation of the two ester groups.

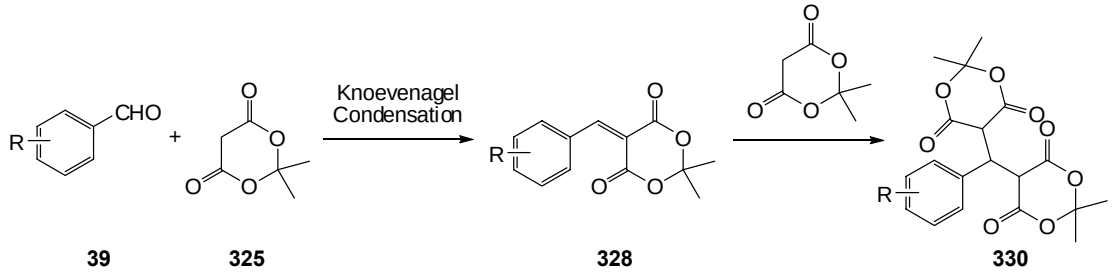
328
E = -10.28

329
E = -10.04

Figure 8 Electrophilicity parameters of **328** and **329**

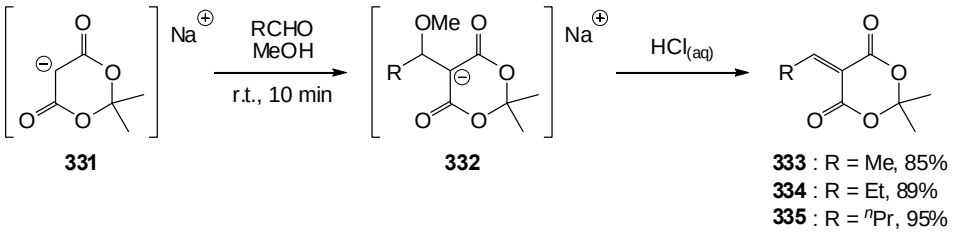
3.1.2 Synthesis of Alkylidene Meldrum's Acid Derivatives

The synthesis of alkylidene MA derivatives **328** is achieved by the Knoevenagel condensation of MA and aldehydes. The condensation reaction can be complicated by the Michael addition of another molecule of MA to the newly formed alkylidene MA to give the bis-adduct **330** (Scheme 112).



Scheme 112 Knoevenagel condensation of benzyaldehydes and Meldrum's acid

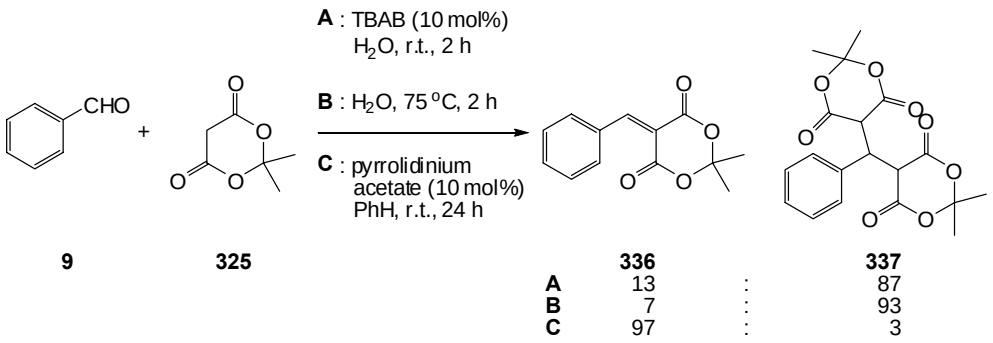
A number of conditions for this Knoevenagel condensation have been reported with a view to increasing the substrate scope of this reaction. One method of avoiding bis-adduct formation is the addition of a nucleophile, such as a methoxide,[15] an amines[16] or a thiols,[17] to alkylidene MA derivatives; the newly formed adduct is then transformed into the desired alkylidene at the end of the reaction (Scheme 113). Although effective, in light of step and atom economy, this is an unattractive process.



Scheme 113 Synthesis of alkylidene MA's in methanol

Other methods for the synthesis of alkylidene MA's include the use of ionic liquids,[18,19] microwave irradiation,[20] amines supported on silica gel,[21] surfactants[22] and simply heating the two components in water.[23] Fillion *et al*. reported a general synthesis of alkylidene MA's using pyrrolidinium acetate as a catalyst (10 mol%) in benzene.[24] By this method,

Fillion successfully synthesised **336** from benzaldehyde in 85% yield, a significant result as under all other conditions **336** undergoes Michael addition of MA (Scheme 114).

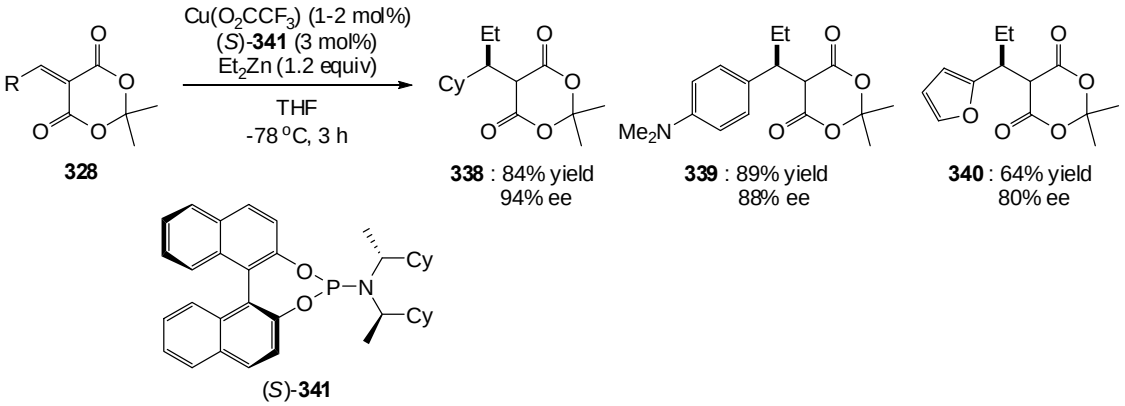


Scheme 114 Synthesis of alkylidene MA derivative **336**

3.1.3 Michael Addition to Alkylidene Meldrum's Acid Derivatives

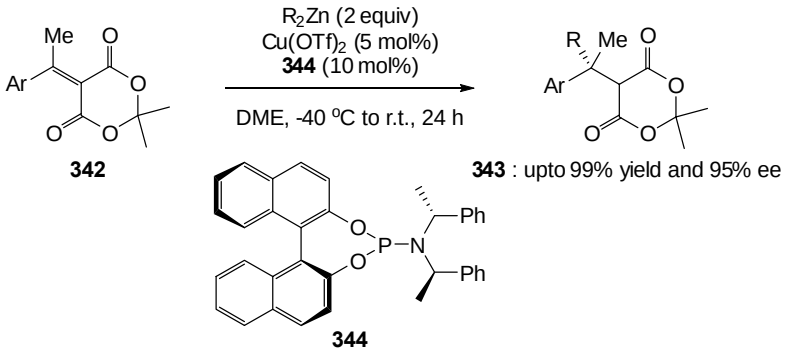
Michael addition to alkylidene MA derivatives has been a key step in a number of multicomponent reactions; MA is reacted with an aldehyde and the desired nucleophile, typically a vinyl ether, enolate or indole.[5] Copper-catalysed additions of Grignard reagents proceeded smoothly,[25-27] however, more recently, research has focused on the addition of terminal alkynes, dialkylzinc reagents and vinylstannanes to alkylidene MA derivatives.

Alkylation of alkylidene MA derivatives by asymmetric copper-catalysed conjugate addition of diethylzinc was reported by Carreira *et al*. using BINOL-derived chiral phosphoramidite **341**.[28] High yields and enantioselectivities were observed with both aliphatic and aromatic substitutents on the alkylidene MA; aliphatic substitutents were found to be the most favourable (Scheme 115).

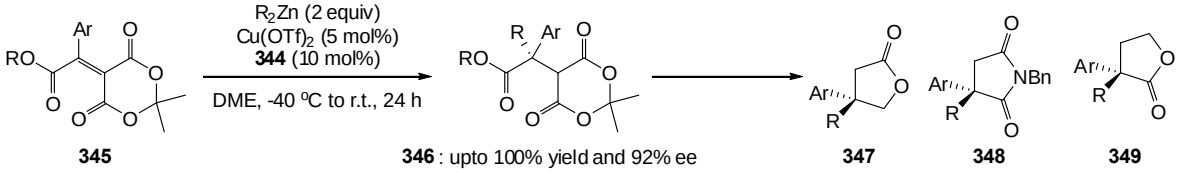


Scheme 115 Asymmetric copper-catalysed alkylation of alkylidene MAs

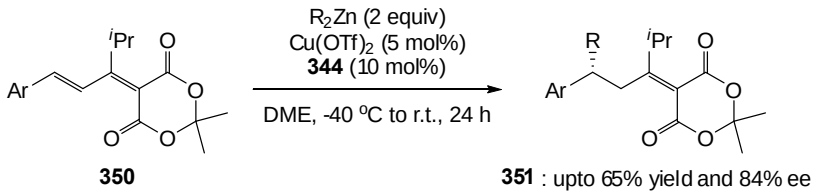
Fillion *et al*. also used copper ligated with BINOL derived chiral phosphoramidites for the asymmetric alkylation of β,β'-disubstituted alkylidene MA derivatives with dialkylzinc reagents; excellent yields and enantioselectivities of up to 95% were observed (Scheme 116).[29] Wilsily and Fillion later reported the expedient preparation of succinimides, succinate esters and acids, γ-butyrolactones and β-amino acid derivatives using this methodology (Scheme 117).[30] This process was extended to the 1,6-conjugate addition of dialkylzinc reagents to α,β,γ,δ-unsaturated MAs **350** which saw a drop in yields and enantioselectivities (Scheme 118).[31]



Scheme 116 Copper-catalysed conjugate addition of dialkylzinc reagents giving all-carbon quaternary centres

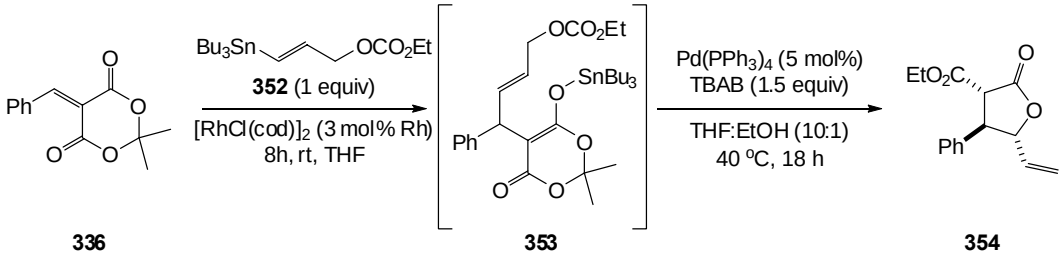


Scheme 117 Addition of dialkylzinc reagents to 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)aryl acetates



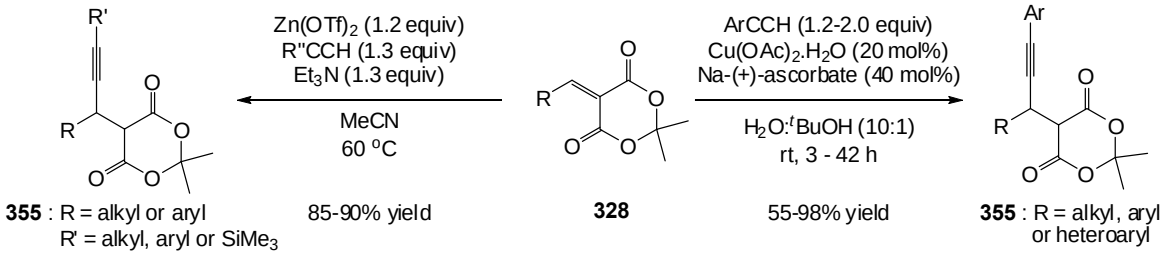
Scheme 118 1,6-conjugate addition of dialkylzinc reagents

Fillion *et al*. synthesised more complex γ-butyrolactones *via* a sequential Rh(I)/Pd-catalysed 1,4-addition/intramolecular allylation.[32] This process was initiated by the Michael addition of vinylstannanes to alkylidene MA **336**. This was followed by the palladium-catalysed allylic *O*-alkylation and ring opening by ethanol to give the desired γ-butyrolactone (Scheme 119).



Scheme 119 Sequential Rh(I)/Pd-catalysed 1,4-addition/intramolecular allylation

Alkynylation of alkylidene MA derivatives was first achieved using trimethylsilylethynyl magnesium bromide[33] and later lithium phenylalkynylide.[34-36] However, Carreira *et al*. have developed a powerful technique which enables the direct use of terminal alkynes without the need for a separate metallation step.[37-41] Copper- and zinc-catalysed conjugate addition of terminal alkynes to alkylidene MA derivatives have been reported giving adducts in high yields (Scheme 120). Copper-catalysed additions of terminal alkynes are carried out in aqueous media.



355 : R = alkyl or aryl
R' = alkyl, aryl or $SiMe_3$

85-90% yield

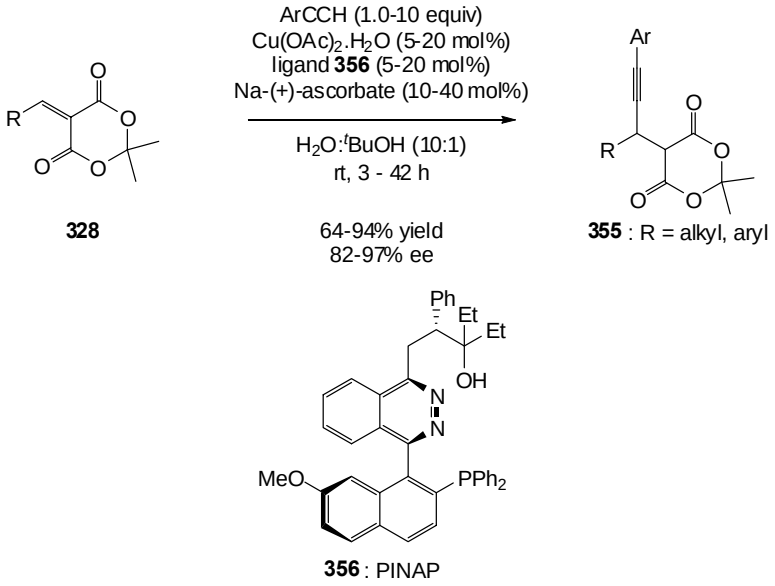
328

55-98% yield

355 : R = alkyl, aryl or heteroaryl

Scheme 120 Zinc- and copper-catalysed alkynylation of alkylidene MAs

Asymmetric alkynylation of alkylidene MA derivatives was not achieved under zinc catalysis, however, excellent enantioselectivities were achieved with copper catalysis. Carreira *et al*. developed the novel chiral P,N-ligand **356** (PINAP) from QUINAP for this transformation; excellent enantioselectivities were achieved for the addition of aromatic alkynes to alkylidene MA derivatives (Scheme 121).[38,40]



328

64-94% yield
82-97% ee

355 : R = alkyl, aryl

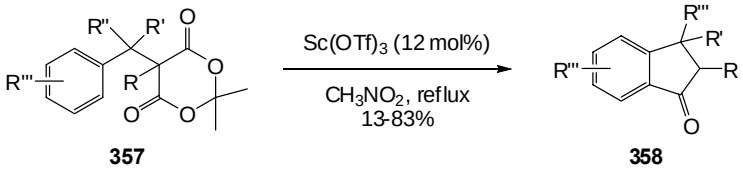
356 : PINAP

Scheme 121 Asymmetric alkynylation of alkylidene MAs

3.1.4 Meldrum's Acids as Acylating Agents

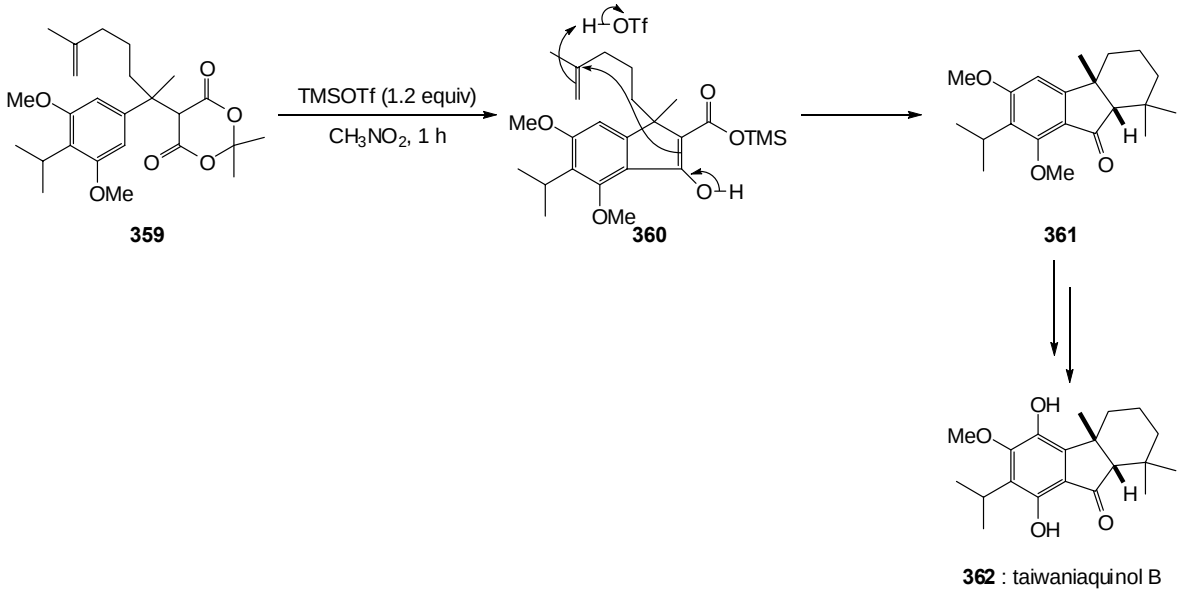
Fillion *et al*. have pioneered the use of 5-mono- and 5,5'-dialkyl-MAs as acylating agents in the catalytic intramolecular Friedel-Crafts reaction. Initial studies showed scandium triflate to be a suitable Lewis acid catalyst for the synthesis of polysubstituted 1-indanones, while trimethylsilyl triflate and triflic acid were also able to catalyse the transformation.[42,43]

Substitution at the α- and/or β-carbons of the substrates were found to be essential for maintaining good yields (Scheme 122). Fillion and Fishlock used this methodology in the synthesis of (±)-taiwaniaquinol B **362**.[44] The formation of the tricyclic core *via* a domino trimethylsilyl triflate catalysed Friedel-Crafts acylation/carbonyl α-*tert*-alkylation reaction was the key step in the synthesis (Scheme 123).



357 **358**

Scheme 122 Intramolecular $Sc(OTf)_3$-catalysed Friedel-Crafts acylation

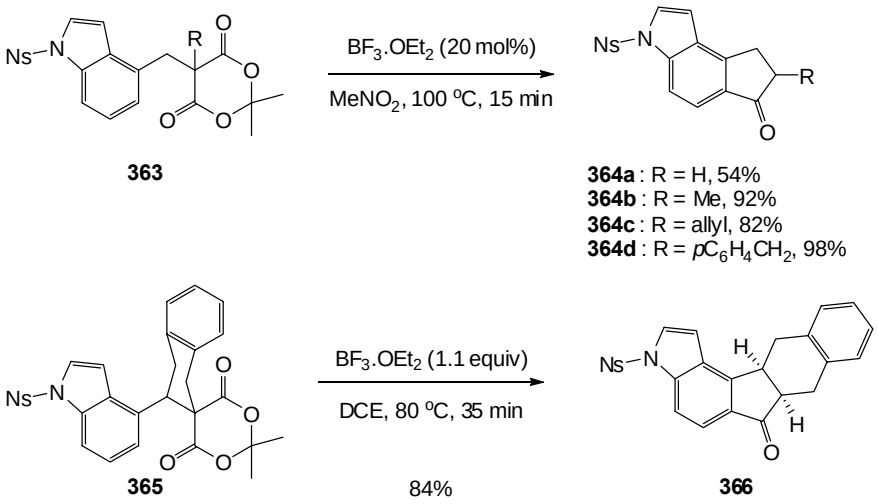


359 **360** **361**

362 : taiwaniaquinol B

Scheme 123 Fillion's synthesis of taiwaniaquinol B

Fillion and Dumas synthesised fused 4,5-disubstituted indole ring systems by an intramolecular Friedel-Crafts acylation of *N*-nosyl-4-substituted indoles.[45] Selective acylation at the 5 position was observed giving the desired tricyclic products under Lewis acid catalysis by boron trifluoride etherate. Both 5-mono and 5,5'-dialkyl MAs cyclised in high yields with pentacyclic **366** being accessed in 84% yield from spiro MA derivative **365** (Scheme 124).



Scheme 124 Synthesis of fused 4,5-disubstituted indole ring systems

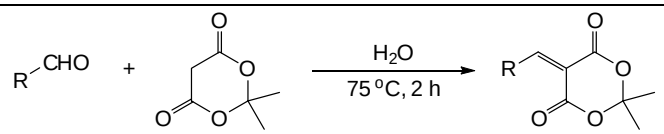
3.2 Synthesis of Alkylidene Meldrum's Acid Derivatives

Due to their synthetic utility, a range of alkylidene MA derivatives was synthesised using the convenient procedure proposed by Bigi *et al*..[23] This uncatalysed procedure was carried out in water, giving the desired product as a precipitate on cooling of the reaction mixture. All products are easily purified by recrystallisation from hot ethanol giving highly coloured crystalline solids.

Good yields were observed for a range of aldehydes with both electron-donating and electron-withdrawing substituents being tolerated (Table 6). This can be rationalised by considering the transformation as a two step process. Electron-deficient aldehydes favour the initial nucleophilic attack of MA, while electron-rich substituents facilitate the loss of water giving the conjugation stabilised olefin.

Pleasingly, a range of heteroatoms was tolerated under the reaction conditions (Table 6, entries 1-3). A lower yield was observed with sterically bulky 2,3,4-trimethoxybenzaldehyde (entry 9). A disappointing 48% yield was observed for the formation of **328k** (entry 11).

Table 6 Synthesis of alkylidene MA's



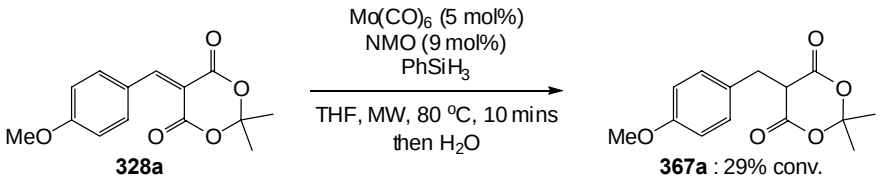
39 **325** **328a-k**

entry	R	product	yield, %[b]
1	4-(OMe)C_6H_4	**328a**	72
2	4-(SMe)C_6H_4	**328b**	75
3	4-(NMe_2)C_6H_4	**328c**	92
4	3,4-(OCH_2O)C_6H_3	**328d**	82
5	2,3-(OCH_2O)C_6H_3	**328e**	73
6	C_6H_5CHCH	**328f**	87
7	3,4-($OMe)_2C_6H_3$	**328g**	81
8	2,5-($OMe)_2C_6H_3$	**328h**	73
9	2,3,4-($OMe)_3C_6H_2$	**328i**	69
10	4-(NO_2)C_6H_4	**328j**	83
11	4-(OBn)C_6H_4	**328k**	48

[a] Reaction conditions : aldehyde (1 equiv.), Meldrum's acid (1.1 equiv.), H_2O, 75 °C, 2 h. [b] Isolated yields after recrystallisation.

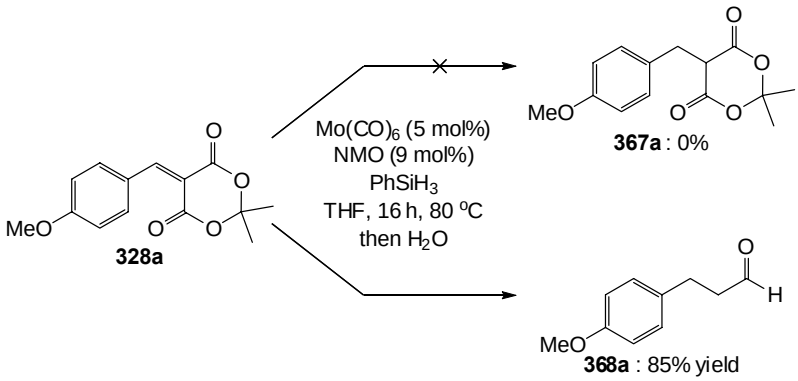
3.3 Reduction of Meldrum's Acid Arylidenes

Alkylidene MA **328a** was exposed to the molybdenum-catalysed reductive conditions developed for the reduction of dimethyl itaconate (*cf.* 2.2.2). The reaction mixture was heated to 80 °C for 10 minutes by microwave irradiation. After hydrolysis of the reaction mixture, a 29% conversion (determined by ^{1}H NMR) to 5-monoalkyl MA **367a** was observed (Scheme 125).



Scheme 125 Molybdenum-catalysed conjugate reduction of **328a**

To investigate this process further the reaction was repeated with an extended reaction time of 16 hours (the reaction being carried in an oil bath). After hydrolysis of the reaction mixture, crude ^{1}H NMR analysis did not show the *gem*-dimethyl peaks of **328a** (1.76 ppm) or **367a** (1.72 and 1.48 ppm), suggesting complete consumption of **328a** and no formation of **367a**. The major peaks present in the crude ^{1}H NMR, along with the two aromatic doublets and the singlet present for the methoxy group, were a 1H triplet at 9.81 ppm (J = 1.5 Hz), a 2H triplet at 2.91 ppm (J = 7.2 Hz) and a 2H multiplet at 2.78-2.72 ppm suggesting the formation of an aldehyde. Purification by flash column chromatography revealed β-aryl aldehyde **368a** as the sole product of the reaction in an 85% yield (Scheme 126). Interestingly, no over-reduction of aldehyde **368a** to 3-(4-methoxyphenyl)propan-1-ol was observed. Keinan had previously reported that aldehyde reduction occurs under his molybdenum-catalysed reductive conditions,[46] suggesting that the aldehyde functionality is protected against reduction until hydrolysis.



Scheme 126 Molybdenum-catalysed synthesis of aldehyde **368a**

This is a completely novel transformation, previous reports of the reduction of benzylidene MAs resulted in high yields of 5-monoalkyl MA derivatives. Reductants for this process include sodium hydrogen telluride,[47] borane•dimethylamine complex,[48] triethylammonium formate,[49] $NaBH_4$[50, 51] and $NaBH_3CN$.[42]

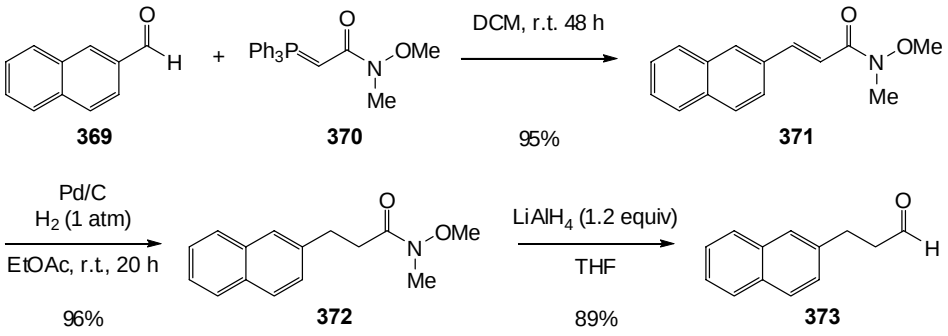
This novel transformation can be described as the two-step, two-carbon homologation of aldehydes.

3.3.1 Synthesis of β-Substituted Propionaldehydes

Beyond dihydrocinnamaldehyde, there are few commercially available β-substituted propionaldehydes. Other reported routes to β-substituted propionaldehydes often involve the reduction of dihydrocinnamates using DIBAL-H or the oxidation of 3-substituted propan-1-ols by a Swern oxidation or by PCC.[52] Reduction of carboxylic acid derivatives to aldehydes using DIBAL-H can be capricious with some substrates lacking reactivity and the over-reduction to the corresponding alcohol being a common drawback. In addition, DIBAL-H ignites upon prolonged exposure to air and reacts violently with water. The oxidising agents mentioned above involve the use of toxic and environmentally damaging reagents.

An alternative route to β-substituted propionaldehydes is the hydroformylation of styrene and its derivatives. Although the oxo process is highly developed, the hydroformylation of styrene often favours the formation of α-phenylpropanal.[53] A recent paper from Zhang *et al*. has reported the highest linear-selectivity for the hydroformylation of styrene with a linear:branched ratio of up to 22:1.[54]

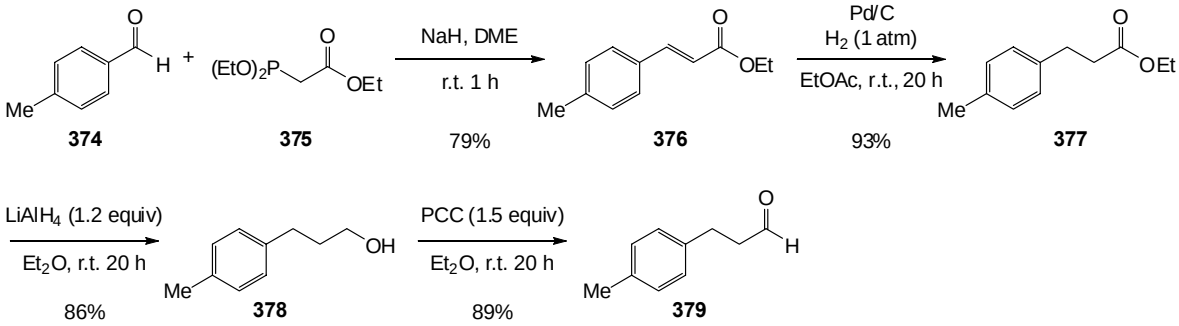
A comparable protocol involving the two-carbon homologation of aldehydes was reported by Lee and Jones in which 1-naphthaldehyde is converted to 3-(1-naphthyl)propanal **373** in three steps.[55] Weinreb amide **371** was formed from 1-naphthaldehyde and *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidine)acetamide **370**.[56] Alkene hydrogenation and reduction of the Weinreb amide with $LiAlH_4$ gave the desired aldehyde **373** (Scheme 127).



369 **370** **371** **372** **373**

Scheme 127 Three-step, two-carbon homologation of 1-naphthaldehyde

Ylide chemistry was also employed by Wallsgrove *et al*. in the multi-step synthesis of 3-(4-methylphenyl)propanal **379**: the β-substituted propionaldehyde was accessed from 4-methylbenzaldehyde **374** in a 56% overall yield (Scheme 128).[57a] This synthetic route was later used by Faber *et al*. for the synthesis of 3-(4-halophenyl)propanals.[57b]



374 **375** **376** **377** **378** **379**

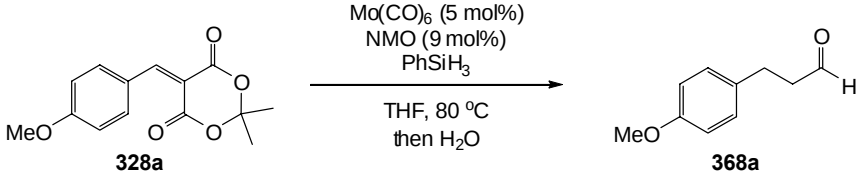
Scheme 128 Four-step, two-carbon homologation of 4-methylbenzaldehyde

3.3.2 Optimisation

It has already been established that molybdenum-catalysed conjugate reductions require heating in THF for good reaction efficiency, for that reason, no temperature or solvent screen was carried out for this novel transformation (*cf*. 2.2).

A decrease in aldehyde formation was observed with shorter reaction times (Table 7). In all cases complete consumption of alkylidene MA **328a** was observed with 5-monoalkyl MA **367a** being the only other product observed.

Table 7 Time dependence of the molybdenum-catalysed synthesis of aldehydes



entry	time, h	yield, %[b]
1	2	48
2	4	65
3	8	77
4	16	85

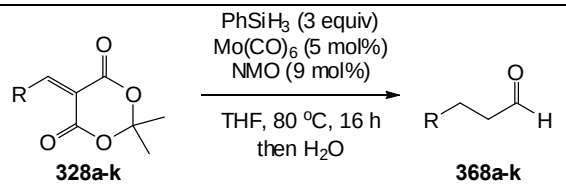
[a] Reaction conditions : **328a** (1.0 equiv.), phenylsilane (3.0 equiv.), $Mo(CO)_6$ (5 mol%), *N*-methylmorpholine *N*-oxide (9 mol%), THF, 80 °C. [b] Isolated yields.

The use of less reactive silanes (Ph_2SiH_2, Et_3SiH and PMHS) gave no reduction, while reducing the equivalents of phenylsilane from three to two equivalents led to a lower yield of 49%. A lower yield of 43% and more complex reaction mixture was observed when the additive NMO was removed from the reaction mixture.

3.3.3 Exploring the Scope of the Reaction

Having established the basis for a useful new functional group transformation, different alkylidene MA derivatives were exposed to the reaction conditions (Table 8).

Table 8 Synthesis of 3-substituted propionaldehydes



328a-k **368a-k**

entry	R	product	yield, %[b]
1	4-(OMe)C_6H_4	**368a**	85
2	4-(SMe)C_6H_4	**368b**	66
3	4-(NMe_2)C_6H_4	**368c**	81
4	3,4-(OCH_2O)C_6H_3	**368d**	65
5	2,3-(OCH_2O)C_6H_3	**368e**	78
6	C_6H_5CHCH	**368f**	39
7	3,4-($OMe)_2C_6H_3$	**368g**	59
8	2,5-($OMe)_2C_6H_3$	**368h**	76
9	2,3,4-($OMe)_3C_6H_2$	**368i**	48
10	4-(NO_2)C_6H_4	**368j**	37
11	4-(OBn)C_6H_4	**368k**	45

[a] Reaction conditions : **328** (1.0 equiv.), phenylsilane (3.0 equiv.), $Mo(CO)_6$ (5 mol%), *N*-methylmorpholine *N*-oxide (9 mol%), THF, 80 °C, 16 h. [b] Isolated yields.

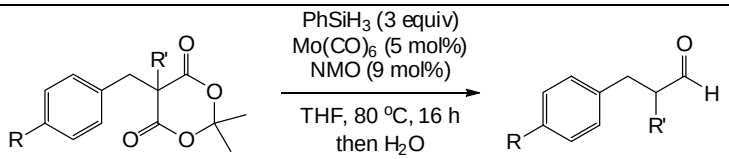
Pleasingly, a number of heteroatoms were tolerated in this process giving the desired aldehydes in high yields (Table 8, entries 1-3). Isolated yields were consistently good for a range of substrates containing electron-donating aryl substituents, with the exception of the sterically hindered **368i** (entry 9). A poor yield was observed for the synthesis of electron-poor **368j**, this observation can be rationalised by the inductive deactivation of the alkylidene MA derivative to the initial conjugate reduction by the electron-withdrawing *para*-nitro group (entry 10). An unexpectedly low yield of 45% was observed for the

formation of **368k** (entry 11). A poor yield of 39% and incomplete consumption of starting material was observed with α,β,γ,δ-unsaturated **328f**, however, no hydride addition to the δ-carbon was observed (entry 6).

3.3.4 Reduction of 5-Monoalkyl and 5,5'-Dialkyl Meldrum's Acid Derivatives

To investigate the scope of the reaction further, alkylated MA derivates **367j**, **367a** and **380** were exposed to the reductive conditions. Nitrophenyl substituted aldehyde **368j**, which had previously been isolated in a poor 37% yield, was accessed in 91% yield from **367j** (Table 9, entry 1). This suggests that the reduction of **328j** is limited by the slow conjugate reduction of its deactivated alkene. Monoalkylated **367a** was reduced in good yield (Table 9, entry 2), however, ^{1}H NMR analysis showed that **380** was unaffected by the reductive conditions (Table 9, entry 3).

Table 9 Reduction of alkylated MAs



entry	substrate	R	R'	product	yield, %[b]
1	**367j**	NO_2	H	**368j**	91
2	**367a**	OMe	H	**368a**	72
3	**380**	OMe	Me	**381**	0

[a] Reaction conditions : Substrate (1.0 equiv.), phenylsilane (3.0 equiv.), $Mo(CO)_6$ (5 mol%), *N*-methylmorpholine *N*-oxide (9 mol%), THF, 80 °C, 16 h. [b] Isolated yields.

3.3.5 Exploring Other Electrophiles

Following the successful quenching of the reaction mixture with water, a number of different electrophiles were used to quench the reaction mixture using alkylidene MA **328a** as the substrate. Bromination was attempted using both bromine and *N*-bromosuccinamide, however, after aqueous work-up propionaldehyde **368a** was the only observed product with no bromine incorporation. The same result was observed when methyl iodide was added to the reaction mixture after 16 hours.

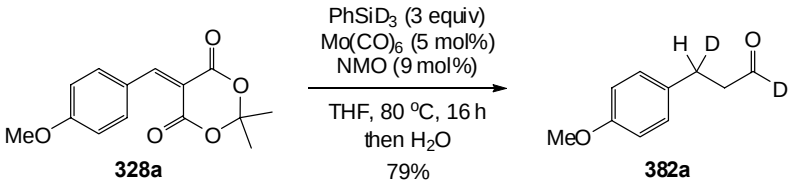
3.3.6 Mechanistic Studies

The formation of 5-monoalkyl MA when reaction times are shortened shows the synthesis of β-substituted propionaldehydes from alkylidene MA derivatives is initiated by a molybdenum-catalysed conjugate reduction. It was postulated that the newly formed enolate is the key intermediate for the transformation, which is supported by the study into 5-mono and 5,5-dialkyl MAs. It is, therefore, due to the fixed keto form of 5,5'-dialkyl MA **380** that no aldehyde formation is observed, while easily enolisable 5-monoalkyl MA derivatives readily form the desired product.

3.3.6.1 Deuterium Labelling Studies

To investigate this novel transformation further, deuterium labelling studies were carried out. Firstly, **328a** was reduced using trideuteriophenylsilane[58] as the terminal reductant. On hydrolysis of the reaction mixture and isolation of the product, NMR analysis showed that there was no aldehyde peak present in the ^{1}H NMR spectra at 9.81 ppm (Figure 10). However, in the ^{2}D NMR spectra there was a singlet present at 9.75 ppm (Figure 9). ^{13}C NMR analysis showed a triplet at 201.9 ppm (J = 26 Hz) and IR bands were observed at 2081 cm^{-1} (C-D) and 1712 cm^{-1} (C=O), suggesting the formation of a deuteroaldehyde. A change in the ^{1}H NMR for the ethyl bridge was also observed (Figure 10 and Figure 11). A 1H multiple was observed at 2.92-2.86 ppm and at 2.74 ppm a 2H doublet (J = 7.9 Hz)

were observed. ^{2}H NMR analysis of the product also showed a singlet at 2.81 ppm suggesting deuteration at the β-carbon indicative of the conjugate reduction of **328a** (Figure 9).[46] This analysis suggests the formation of the deuterio-aldehyde **382a** (Scheme 129); this was confirmed by ^{1}H-, ^{2}D- and ^{13}C NMR, mass spectrometry and IR analysis.



Scheme 129 Reduction of **328a** using trideuterophenylsilane

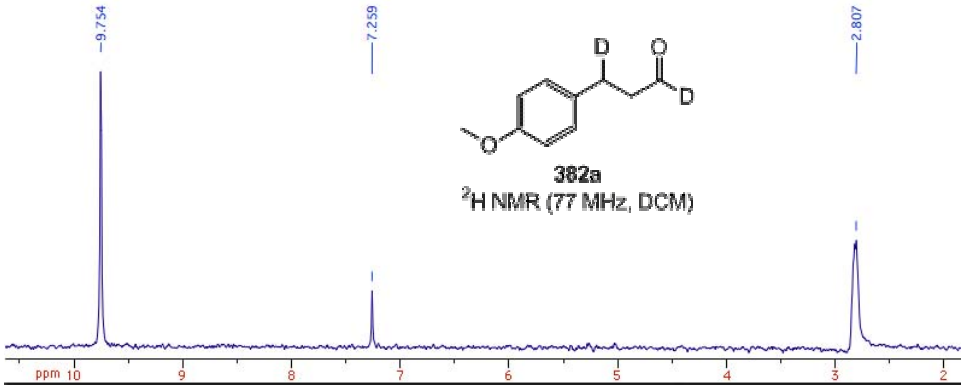


Figure 9 ^{2}D NMR 1,3-dideutero-3-(4-methoxyphenyl)propanal **382a**

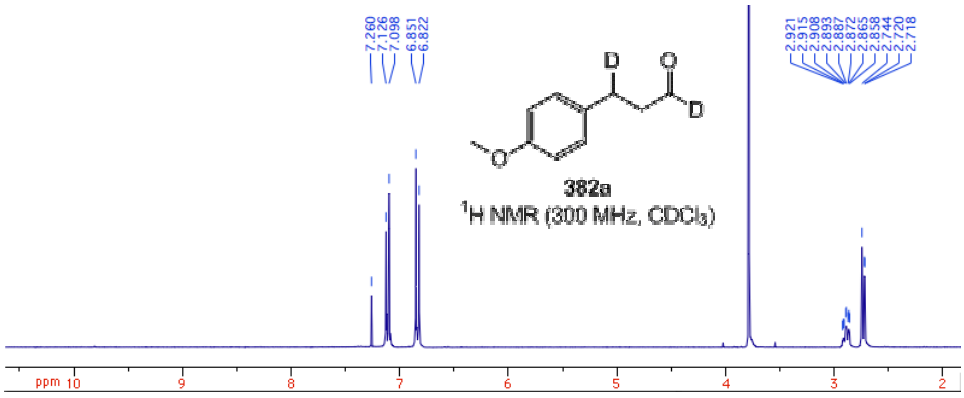


Figure 10 ^{1}H NMR of 1,3-dideutero-3-(4-methoxyphenyl)propanal **382a**

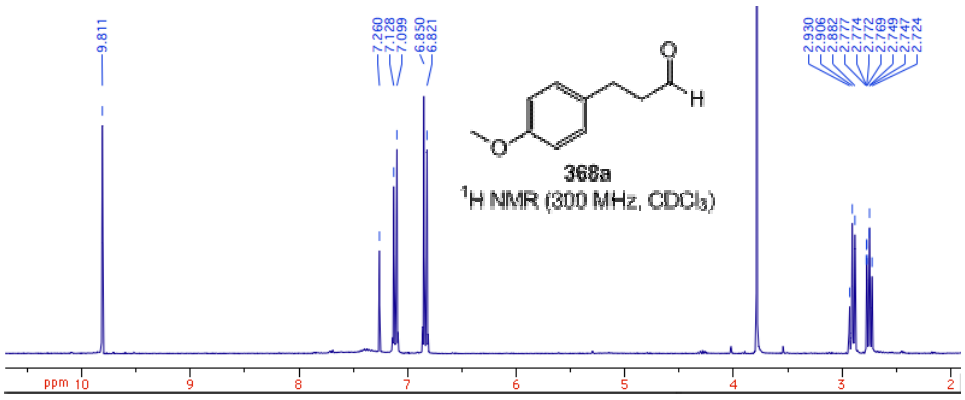
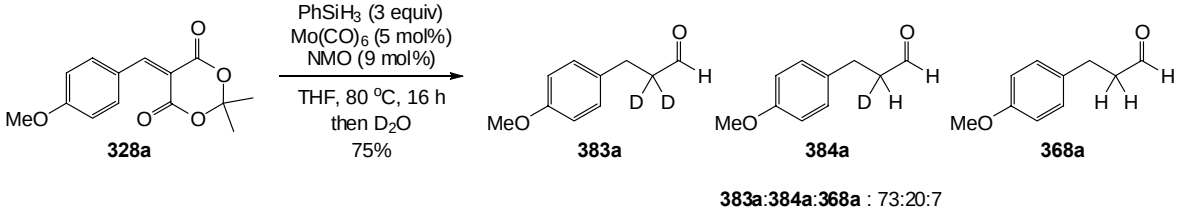


Figure 11 ^{1}H NMR of 3-(4-methoxyphenyl)propanal **368a**

Following the deuterium labelling using trideuteriophenylsilane, the reduction of **328a** with phenylsilane and hydrolysis with deuterium oxide was carried out. The isolated product showed a 1H singlet at 9.81 ppm in the ^{1}H NMR (Figure 13), this is a change from the 1H triplet observed for **368a** at 9.81 ppm (Figure 14), this suggests a α,α'-dideuterated product. The ^{2}D NMR showed only a singlet at 2.64 ppm (Figure 12), confirming deuteration at the α-carbon. The ^{1}H NMR did not show cleanly either mono- or di-deuteration at the α-carbon, a singlet was observed at 2.90 ppm and a multiplet was observed at 2.74-2.71 ppm, these peaks integrated in a ratio of ~5:1 (Figure 13). Mass spectrometry showed the presence of dideuterated **383a**, monodeuterated **384a** and **368a** in a 73:20:7 ratio, which concurs with the integration values (Scheme 130).



Scheme 130 Reduction quenched by deuterium oxide

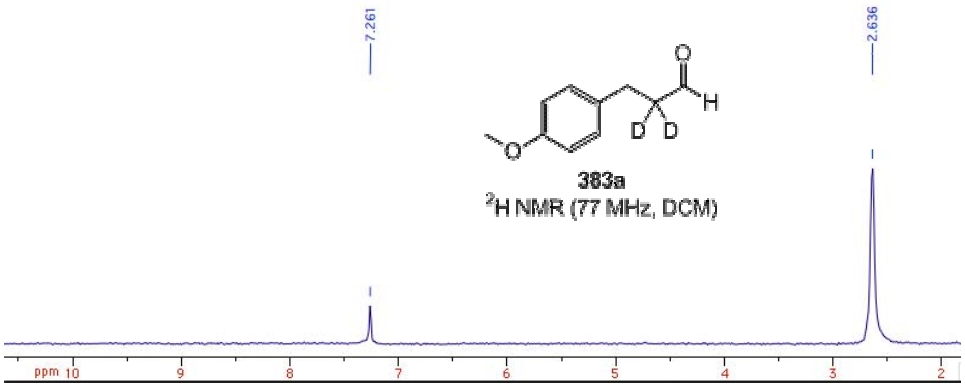


Figure 12 ^{2}D NMR of α,α'-dideutero-3-(4-methoxyphenyl)propanal **383a**

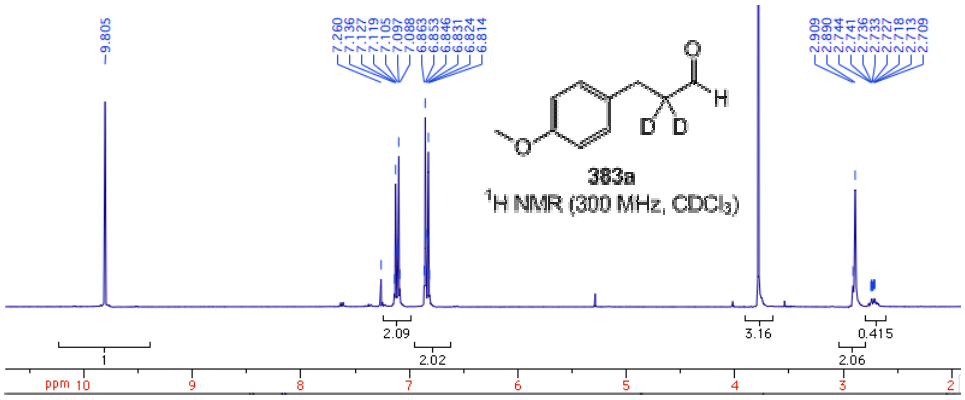


Figure 13 ^{1}H NMR of α,α'-dideutero-3-(4-methoxylphenyl)propanal **383a**

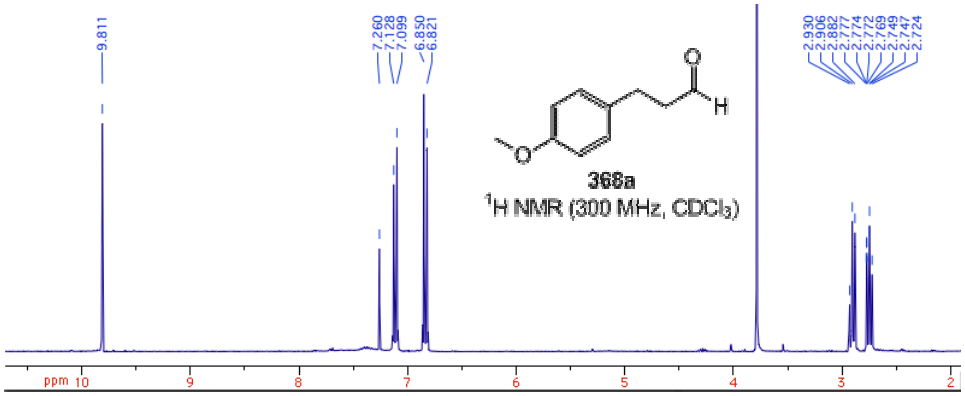
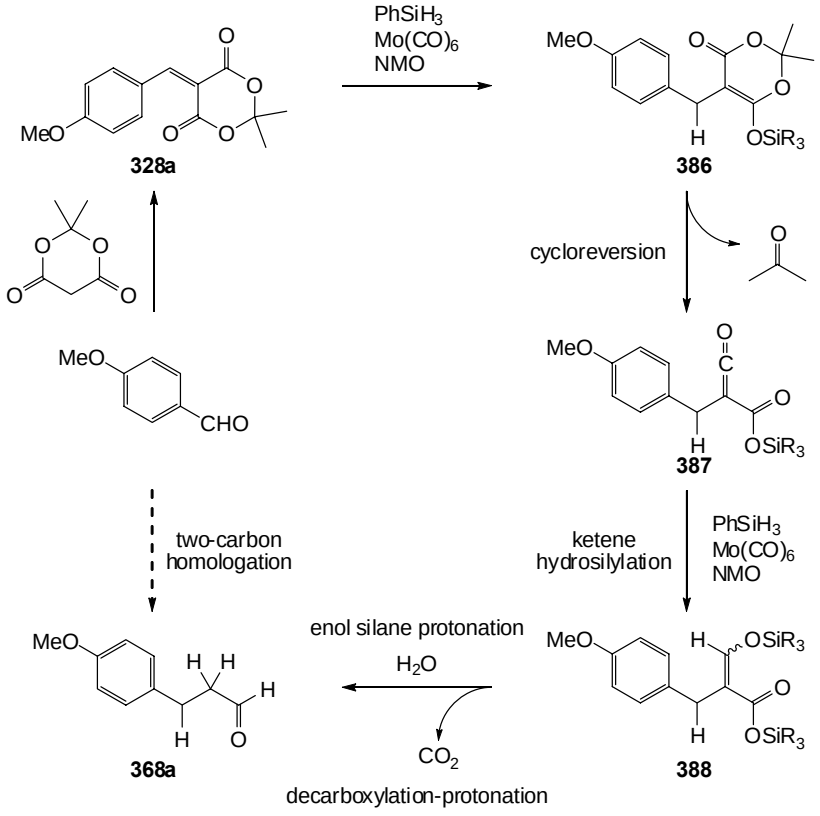


Figure 14 ^{1}NMR of 3-(4-methoxyphenyl)propanal **368a**

3.3.7 Proposed Mechanism

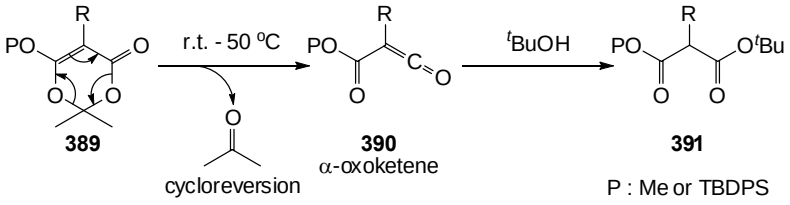
In light of the mechanistic studies, we propose a mechanism in which hydride is delivered to the β-carbon of **328a** by a molybdenum-catalysed hydrosilylation giving dioxinone **386** (Scheme 131). On heating, rapid cycloreversion occurs, eliminating acetone to reveal ketene **387**. It is proposed that the newly formed ketene undergoes hydrosilylation by a second equivalent to phenylsilane to afford enol silane **388**. This intermediate remains in solution, protecting the aldehyde functionality from further reduction, until hydrolysis at the end of reaction. As shown by the deuterium labelling studies, hydrolysis delivers two protons to the α-carbon. The elimination of carbon dioxide on hydrolysis was confirmed by limewater test.



Scheme 131 Proposed mechanism for the two-carbon homologation of aldehydes

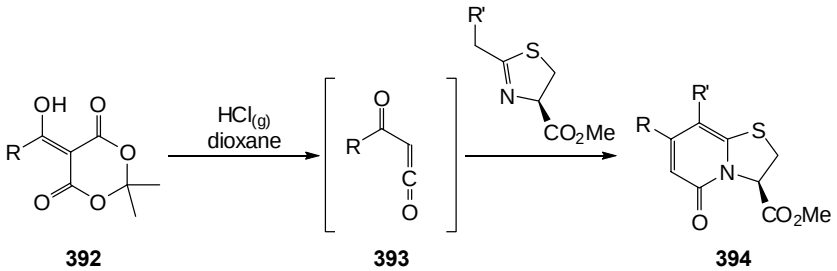
Attempts to observe reaction intermediates by NMR were unsuccessful; however, disappearance of the isopropylene group of MA and appearance of acetone in the reaction mixture was observed when the reaction was carried out in deuterated THF, in a sealed NMR tube. Along with the positive limewater test, this clearly suggests that acetone is eliminated prior to protonation, while carbon dioxide is eliminated on protonation.

A number of important transformations undertaken by Meldrum's acid derivatives can also be attributed to the cyclic malonate's ability to undergo cycloreversion giving α-oxoketenes after elimination of acetone. The synthesis of ketenes from MA derivatives using flash vacuum pyrolysis is well established,[6] however, it was not until 1997 that an efficient, mild method of generating α-oxoketenes was reported by Sato *et al*.[59] IR and ^{1}H NMR spectroscopy provided direct evidence of ketene formation from enolised MA derivatives in the synthesis of linear malonates (Scheme 132).



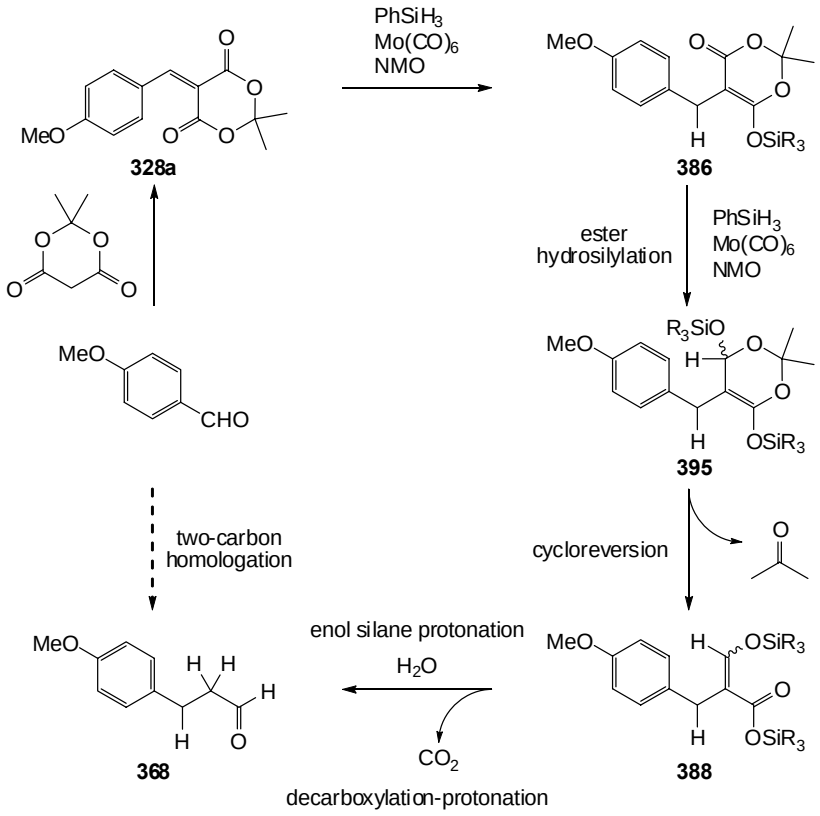
Scheme 132 Generation of α-oxoketenes from enolised MA derivatives

As well as the synthesis of linear malonates, intermediate α-oxoketenes have been used in cyclocondensations with imines in the synthesis of both bicyclic sulfur-containing 2-pyridones and multi-ring fused 2-pyridones (Scheme 133).[60-63] Almqvist *et al*. showed that, under acid conditions 2-pyridones could be synthesised in excellent yields.



Scheme 133 Almqvist's synthesis of bicyclic sulphur-containing 2-pyridones

An alternative mechanism, in keeping with the deuterium-labelling studies, can be envisaged in which α-oxoketene **387** is not formed. Hydrosilylation of the ester moiety of dioxinone **386** could occur to give disilylated **395**, which then undergoes cycloreversion to give intermediate **388** (Scheme 134).



Scheme 134 Alternative mechanism for two-carbon homologation of aldehydes

3.4 Conclusion

We have reported a expeditious two-carbon homologation of aldehydes, catalysed by the cheap, stable $Mo(CO)_6$. Moderate to good isolated yields have been observed for a range of alkylidene MA derivatives with the highest yields being observed with electron-rich olefins. It is proposed that this novel transformation is initiated by the hydrosilylation of the α,β-unsaturated ester, followed by cycloreversion which reveals an α-oxoketene which is, in turn, hydrosilylated. On termination of the reaction, decarboxylative protonation furnishes the desired 3-substituted propionaldehyde.

The proposed mechanism is supported by deuterium labelling studies in which deuterium has been used as both an electrophile, in the form of deuterium oxide, and as a nucleophile, in the form of trideuteriophenylsilane.

3.5 References

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Chapter 4 - Amine Promoted Reduction of Malonic Esters to β-Substituted Propionaldehydes and γ-Substituted Propylamines

4.1 Lewis Base Catalysis

In a recent, comprehensive review, Denmark and Beutner define Lewis base catalysis as:

"*…the process by which an electron-pair donor increases the rate of a given chemical reaction by interacting with an acceptor atom in one of the reagents or substrates. The binding event may enhance either the electrophilic or nucleophilic character of the bound species. Furthermore, the Lewis base should not be consumed or altered during the course of the reaction – a hallmark of any catalytic process*."[1]

One key application of Lewis base catalysis is the activation of silicon reagents enabling efficient ligand transfer to acceptor electrophiles.

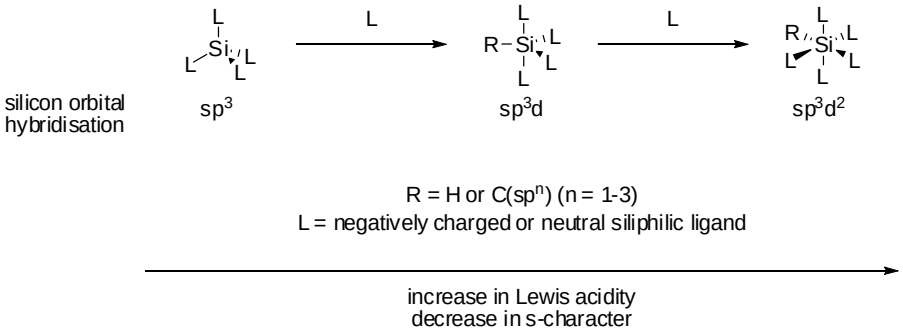
4.1.1 Hypervalent Silicon

In 1809 Gay-Lussac discovered $SiF_4.2NH_3$, the first reported hypervalent silicon reagent.[2] However, it was not until the late 20th century and into the 21st century that the synthetic utility of hypervalent silicon reagents was fully explored. A vast range of stereoselective transformations have been reported with particular attention being paid to Lewis base catalysis, where, through coordination of optically active organic compounds to tetrahedral silicon reagents, highly selective transformations have been achieved.[1, 3-5]

Unlike carbon, in the presence of Lewis bases, silicon can form five-, six- and even seven-coordinated silicon species.[6-8] Two explanations have been proposed for the formation of hypervalent silicon species; firstly, it is due to the participation of silicon's 3d orbitals,[3,5]

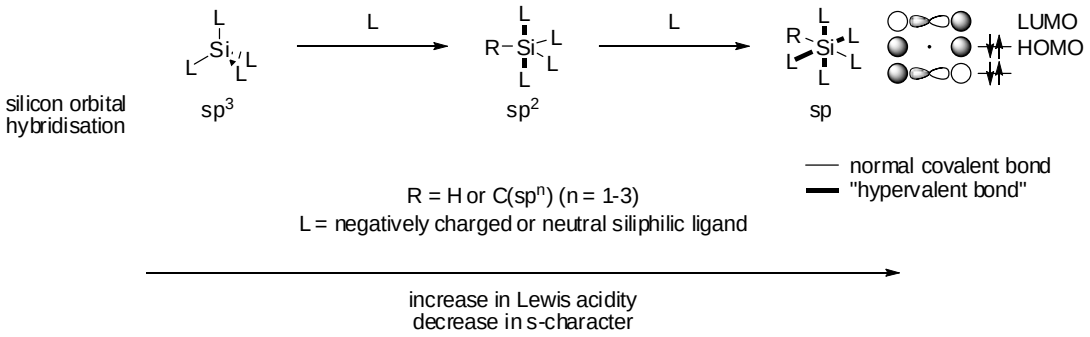
and secondly, it is due to "hypervalent bonding" and the formation of 3-centre-4-electron molecular bonds.[9]

If hypervalency is a consequence of 3d orbital participation then the five-coordinate species would be sp^3d hybridised with trigonal-bipyramidal geometry whilst the six-coordinate species would be sp^3d^2 hybridised with octahedron geometry (Scheme 135). As the s-character of the silicon centre decreases, the Lewis acidity increases and the Si-R bond is elongated leading to efficient hydride or carbon nucleophile transfer to a donor molecule.



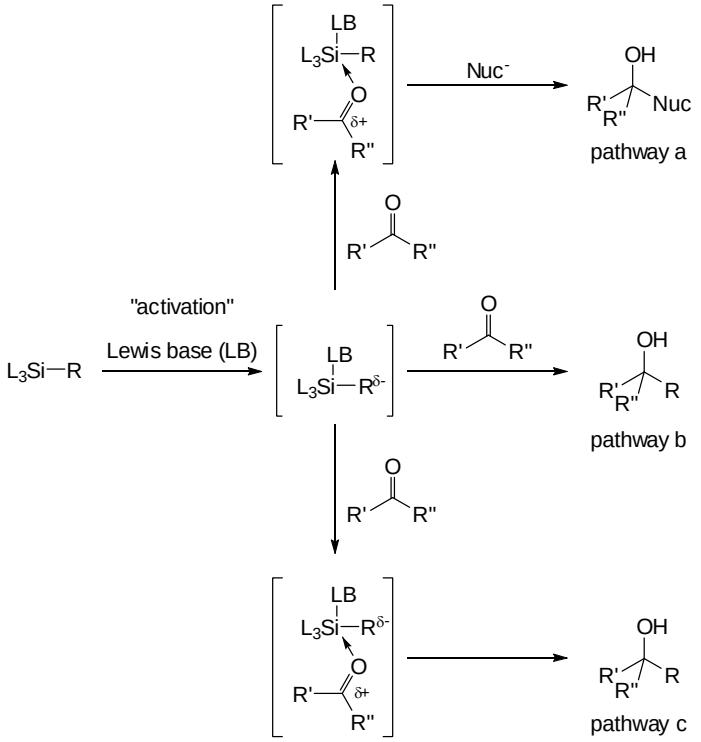
Scheme 135 Participation of 3d-orbitals in hypervalent silicon species

It was Denmark *et al*. who proposed that it is the participation of "hypervalent bonding" and the formation of one (pentavalent) or two (hexavalent) 3-centre-4-electron bonds which enables the formation of hypervalent silicon species, ruling out the participation of the 3d orbitals.[9] The 3-centre-4-electron molecular bonds are formed from a silicon p-orbital and two orbitals from two electronegative ligands, the remaining silicon p-orbitals and s-orbital hybridise and form more conventional covalent bonding. In the case of the hypervalent bonds, the majority of the electron density is placed on the ligands due to the HOMO being a non-bonding interaction. The silicon centre, therefore, increases in s-character and Lewis acidity as the number of hypervalent bonds increases (Scheme 136).



Scheme 136 Formation of "hypervalent bonds" in hypervalent silicon species

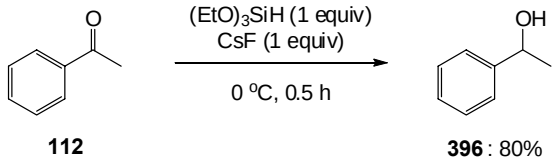
Three different reaction modes are possible with hypervalent silicon reagents. Firstly, it can act as a Lewis acid, activating a substrate to attack from an external nucleophile (Scheme 137, pathway a). Secondly, the nucleophilic ligand of the silicon reagent is transferred to the substrate with no substrate-silicon interaction (Scheme 137, pathway b). The final reaction pathway involves substrate activation by the Lewis acidic silicon reagent with nucleophilic ligand transfer occurring at the same time (Scheme 137, pathway c).



Scheme 137 Reaction modes involving hypervalent silicon species

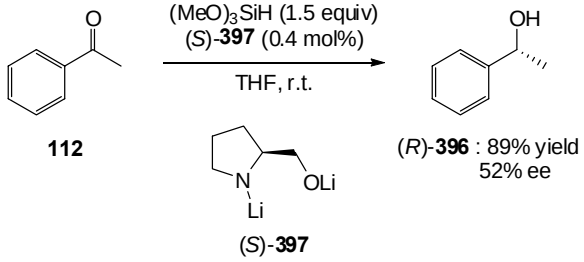
4.1.2 Lewis Base Promoted Reduction of Ketones by Silanes

Corriu *et al*. first recognised the tendency of hypervalent silanes to release hydrides on addition of a Lewis base when he demonstrated the reduction of acetophenone to phenyl ethanol **396** using triethoxysilane and CsF (Scheme 138).[10-12] The addition of CsF was found to be essential as ketones are chemically inert to trialkoxysilanes.



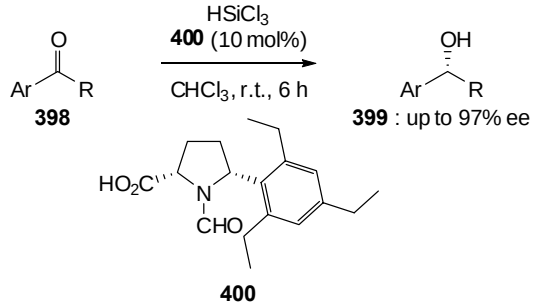
Scheme 138 Fluoride promoted reduction of acetophenone

Activation of silanes by alkoxy ligands enabled the development of asymmetric Lewis base catalysed reductions.[13a] The first example of catalytic asymmetric reduction of ketones by trialkoxysilanes was promoted by the dilithium salts of chiral diols or amino alcohols (Scheme 139).[13b]



Scheme 139 The first asymmetric reduction of ketones using trialkoxysilanes

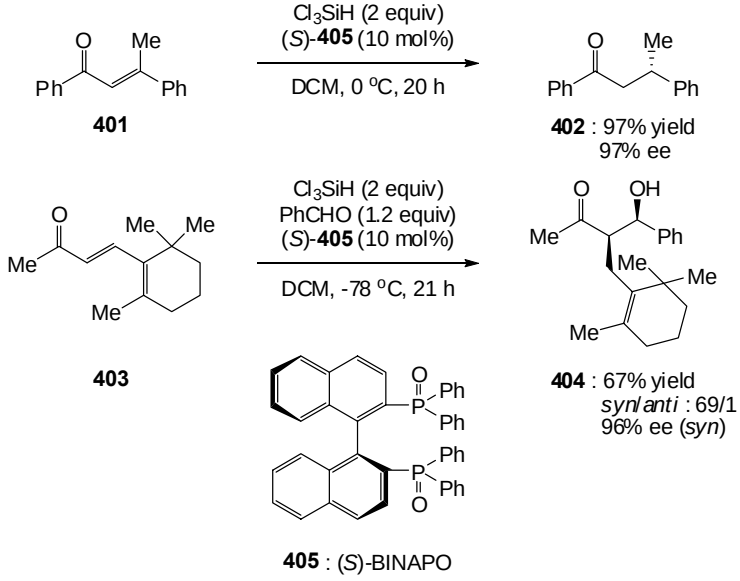
Since the example above (Scheme 139), the development of asymmetric organocatalysis has exploded within organic chemistry. Recent examples of asymmetric ketone reductions give the desired products in excellent yields and enantioselectivities (Scheme 140).[14] Trichlorosilane is often employed in these transformations as a cheap stoichiometric reductant.



Scheme 140 Lewis base promoted ketone reduction

4.1.3 Lewis Base Promoted Conjugate Reduction by Silanes

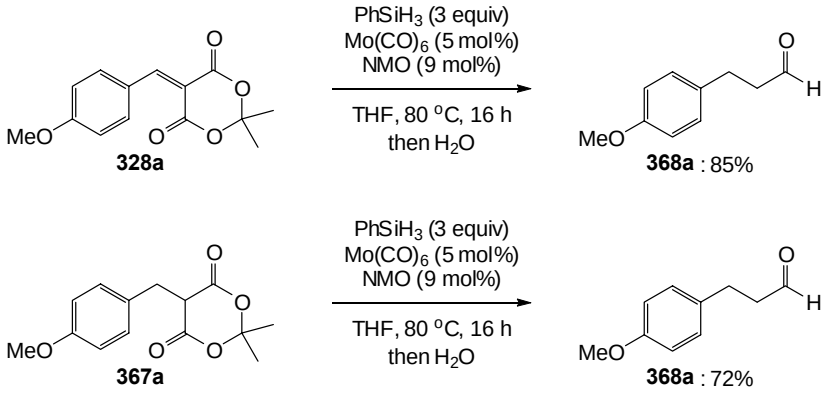
Nakajima *et* al. reported the first example of a Lewis base catalysed conjugate reduction and a reductive aldol reaction.[15] Hexamethylphosphoramide (HMPA) and aryl phosphine oxides, including (*S*)-BINAPO **405**, enabled highly selective asymmetric transformations (Scheme 141). The one-pot reductive aldol reaction is particularly pleasing as benzaldehyde reduction was scarcely observed under the reaction conditions described. The observed stereoselectivities are competitive with many asymmetric transition metal catalysed reductive aldol reactions (*cf*. 1.2).



Scheme 141 (*S*)-BINAPO catalysed asymmetric conjugate reduction and reductive aldol

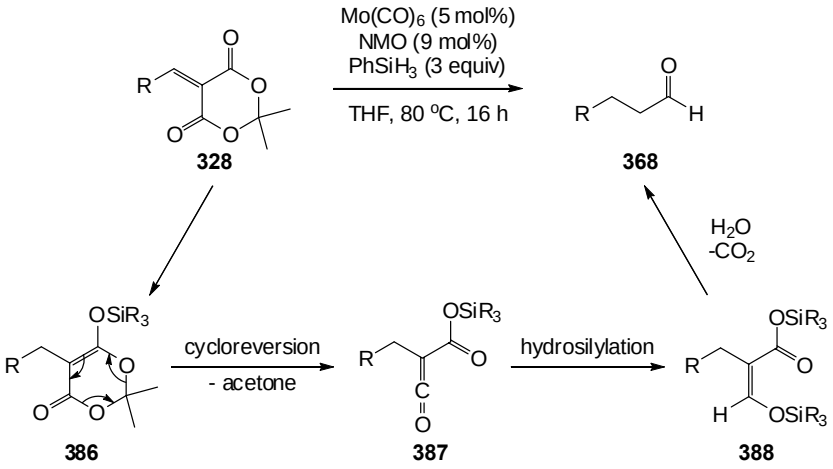
4.2 Reduction of 5-Monoalkyl Meldrum's Acid Derivatives

During previous work into the molybdenum-catalysed two-carbon homologation of aldehydes (*cf*. Chapter 3), it was shown that β-substituted propionaldehdyes **368** could be formed by the reduction of both alkylidene MA derivatives **328** and 5-monoalkyl MA derivatives **367** (Scheme 142). In the latter example the reaction was initiated by enolisation, not a molybdenum-catalysed conjugate reduction.



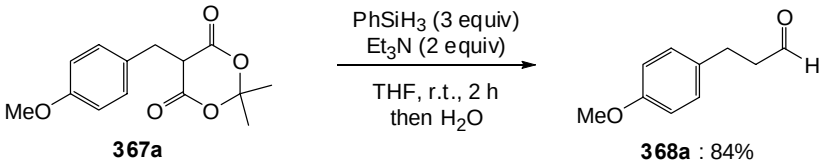
Scheme 142 Molybdenum-catalysed synthesis of β-substituted propionaldehydes

It was proposed that the reaction proceeded *via* α-oxoketene **387**, formed from the cycloreversion of **386** (Scheme 143). This ketene was hydrosilylated to give **388** which, after decarboxylative protonation, gave of the desired aldehyde.



Scheme 143 Proposed mechanism for the molybdenum-catalysed synthesis of β-substituted propionaldehydes

In light of this work, it was postulated that a metal-free variant of this transformation could be carried out using a hypervalent silicon reagent to reduce the cyclic malonate to the desired β-substituted propionaldehyde. In an initial investigation into this Lewis base promoted transformation, 5-monoalkyl MA derivative **367a** was stirred, with phenylsilane and triethylamine, in THF at 80 ^{o}C for 16 hours. ^{1}H NMR analysis of the reaction mixture showed complete conversion of **367a** to 3-(4-methoxyphenyl)propanal **368a**. In the absence of triethylamine no reaction was observed. Pleasingly, complete consumption of **367a** was achieved after two hours at ambient temperature giving **368a** in an 84% isolated yield (Scheme 144).



367a **368a** : 84%

Scheme 144 Triethylamine promoted reduction of **367a**

4.2.1 Optimisation

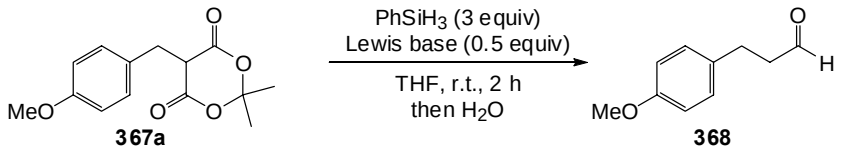
4.2.1.1 Lewis Base Screen

A number of different Lewis bases were screened for this reaction (Table 10). 50 mol% of Lewis base was used in the additive screen, however, it was found that no turnover of catalyst was observed (all conversions were below 50%). Reactivity was observed with all amine bases, excellent conversions were observed for triethylamine and *N*,*N*-dimethylaminopyridine, DMAP (Table 10, entries 1 and 2). Due to increased steric bulk, lower conversions were observed for Hunig's base and diazabicycloundec-7-ene, DBU (entries 4 and 5). A good conversion was observed using *N*-methylmorpholine *N*-oxide (entry 3); activation of silanes using amine-*N*-oxides has been documented in a number of recent reviews.[4] No reactivity was observed on using dicyclohexylurea (DCU), triphenylphosphine, dimethylsulfoxide (DMSO) or dimethylformamide (DMF) as Lewis bases (entries 6-9). Importantly, no reactivity was observed when using potassium

carbonate, illustrating that the role of the base is not only the deprotonation of the substrate but also the activation of the silane (entry 10).

Due to cost and ease of handling, triethylamine was chosen as the preferred Lewis base promoter for this transformation.

Table 10 Lewis base screen



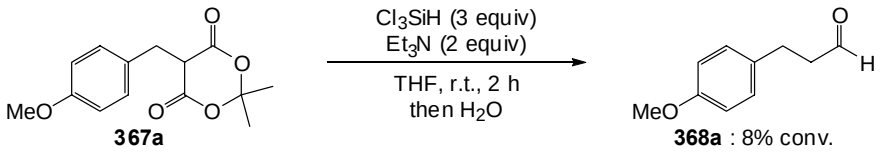
367a **368**

entry	Lewis base	conversion, %[b]
1	Et_3N	49
2	DMAP	49
3	NMO	45
4	DIPEA	40
5	DBU	30
6	DCU	0
7	PPh_3	0
8	DMSO	0
9	DMF	0
10	K_2CO_3	0

[a] Reaction conditions: **367a** (1 equiv), phenylsilane (3 equiv), Lewis base (0.5 equiv), THF, r.t., 2 h.
[b] Conversion determined by ^1H NMR.

4.2.1.2 Silane Screen

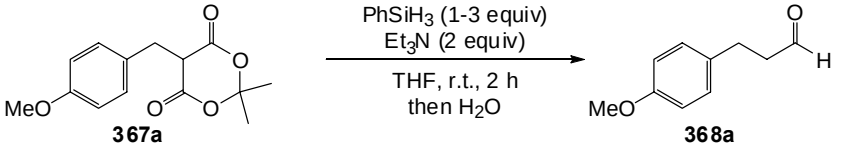
As with the molybdenum-catalysed synthesis of β-substituted aldehydes, less reactive silanes did not result in successful product synthesis. Diphenylsilane, triethylsilane, diethoxymethylsilane and polymethylhydrosiloxane showed no reactivity. The use of trichlorosilane resulted in the formation of **368a** in an 8% conversion (Scheme 145).



Scheme 145 Reduction of **367a** by trichlorosilane

Lower yields were observed on decreasing the equivalents of phenylsilane (Table 11), a yield of less than 50% was observed on using equimolar amounts of 5-monoalkyl MA derivative **367a** and phenylsilane suggesting that 2 equivalents of phenylsilane is required for this transformation.

Table 11 Effect of phenylsilane equivalents on yield

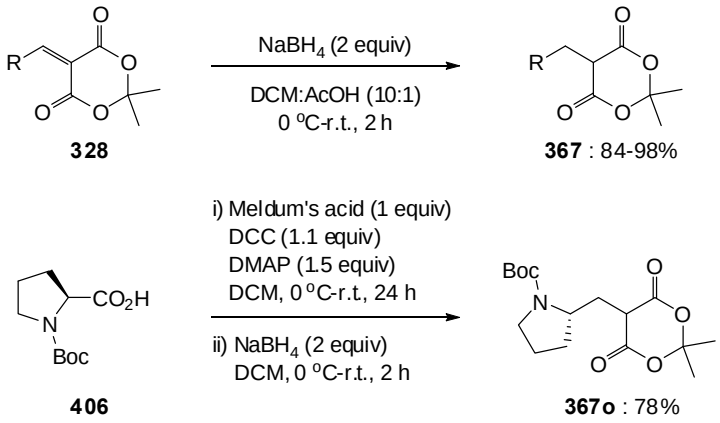


entry	equivalents of $PhSiH_3$	yield, %[b]
1	1	41
2	2	67
3	3	84

[a] Reaction conditions : **367a** (1 equiv), phenylsilane (1-3 equiv), triethylamine (2 equiv), THF, r.t., 2 hours. [b] Isolated yields.

4.2.2 Exploring the Scope of the Reaction

A range of 5-monoalkyl MA derivatives **367** were synthesised in excellent yields from alkylidene MA derivatives **328** by reduction with $NaBH_4$ in high yield.[16] Optically active substrate **329o** was accessed by the reductive coupling MA and Boc-L-Proline **406**.[17]

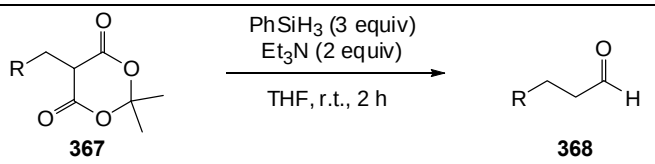


Scheme 146 Synthesis of 5-monoalkyl MAs

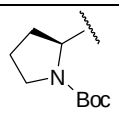
The 5-monoalkyl MA derivatives were exposed to the mild reductive conditions described above resulting in the synthesis of the desired β-substituted propionaldehydes (Table 12), with the exception of **367m** (entry 8). An insoluble salt, which underwent no further transformation, was formed on addition of triethylamine to **367m**, a contrast to its regioisomer **367l** which proceeds smoothly (entry 7).

Moderate to high yields were observed for a range of functionalities. Electron poor **368j** was isolated in the highest yield (entry 2), however, only a moderate yield was observed with aryl halide **368n** (entry 9). A yield of 74% was observed for benzyloxy substituted **368k** (entry 6); this aldehyde was accessed in only 45% yield from the corresponding alkylidene MA derivative **328k** using molybdenum-catalysed reductive conditions (*cf.* 3.3.3).

Table 12 Triethylamine promoted reduction of 5-monoalkyl MA derivatives **367**

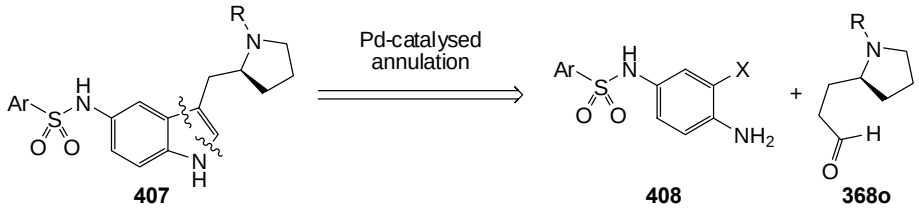


367 **368**

entry	R	product[a]	yield, %[c]
1	4-(OMe)C_6H_4	**368a**	84
2	2,3-(OCH_2O)C_6H_3	**368e**	78
3	C_6H_5CHCH	**368f**	80
4	3,4-$(OMe)_2C_6H_3$	**368g**	61
5	4-(NO_2)C_6H_4	**368j**	92
6	4-(OBn)C_6H_4	**368k**	74[b]
7	2-naphthyl	**368l**	65
8	1-naphthyl	**368m**	0
9	4-BrC_6H_4	**368n**	56
10		**368o**	75

[a] Reaction conditions: **367** (1 equiv), phenylsilane (3 equiv), triethylamine (2 equiv), THF, r.t., 2 h. [b] Reaction was stirred for 4 h. [c] Isolated yields.

Pleasingly, chiral γ-amino aldehyde **368o** was isolated in good yield (entry 10). This γ-amino aldehyde could be used in the synthesis of a range of potent and selective indole based 5-HT_6 receptor agonists and antagonists **407**[18] *via* a palladium-catalysed indole formation with *o*-haloanilines (Scheme 147).[19]

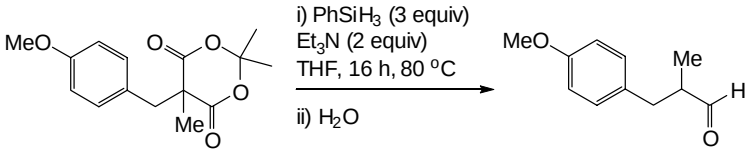


407 **408** **368o**

Scheme 147 Proposed synthetic route to biologically active indole derivatives from **368o**

In addition to 5-monoalkylated MA derivatives, 5,5'-disubstituted MA derivative **380** was exposed to these reductive conditions. Analysis of the reaction mixture showed that, even

after a prolonged period of heating, 5,5'-disubstituted MA derivative **380** underwent no reduction, only unreacted **380** was observed in the reaction mixture (Scheme 148).

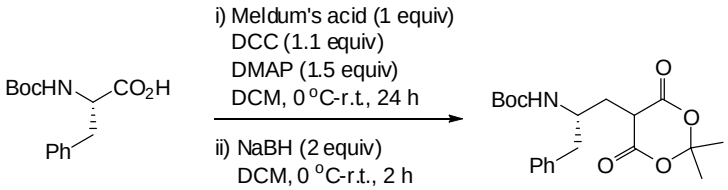


380 **381** : 0%

Scheme 148 Reduction of 5,5'-dialkyl MA **380**

4.2.2.1 Synthesis of Aminoaldehydes

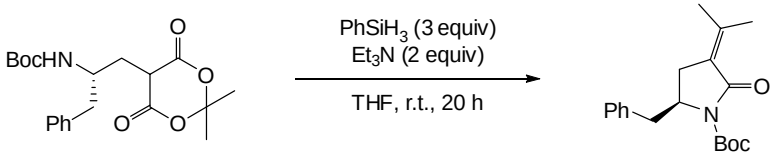
Following the formation of chiral γ-amino aldehyde **368o**, *N*-Boc-L-phenylalanine derivative **367p** was synthesised by the same method as **367o** (Scheme 149).[20]



409 **367p** : 84%

Scheme 149 Synthesis of **367p**

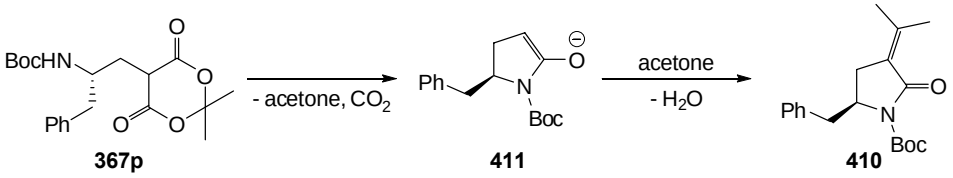
Exposure of this secondary carbamate to the reductive conditions described above did not result in the formation of any amino aldehyde: crude ^{1}H NMR analysis showed no peaks between 9 and 10 ppm. Following purification by flash column chromatography, one and two dimensional NMR studies showed the primary product of the reaction was chiral 2-pyrrolidinone **410**; no other products were isolated from the reaction mixture (Scheme 150).



367p **410** : 45% yield

Scheme 150 Reduction of **367p**

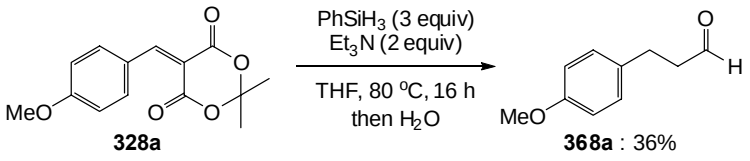
No reaction was observed when either triethylamine or phenylsilane were removed from the reaction mixture. It is proposed that the reaction is initiated by the nucleophilic attack of the nitrogen on the electrophilic ester of the MA group; subsequent elimination of acetone and carbon dioxide results in the formation of enolate **411** (Scheme 151). The eliminated acetone, activated by the Lewis acidic silane species, then undergoes condensation at the 3-position to give **410**.



Scheme 151 Propose route to **410**

4.2.2.2 Reduction of Michael Acceptors

Reduction of alkylidene MA derivative **328a** by triethylamine and phenylsilane was achieved with prolonged heating, and aldehyde **368a** was isolated in a 36% yield (Scheme 152). This transformation is unsurprising in light of high electrophilicity of **328a**[21] and the ability of silanes to reduce Michael acceptors in the presence of Lewis bases (removal of triethylamine from the reaction mixture resulted in no reaction).[15] When less reactive dimethyl itaconate was exposed to the same reductive conditions no conversion to dimethyl 2-methyl succinate was observed.

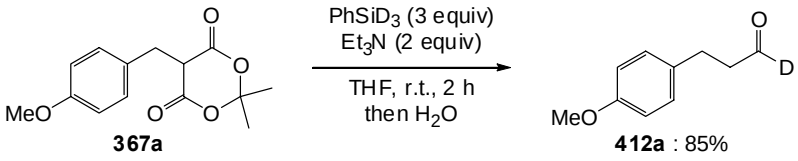


Scheme 152 Triethylamine promoted tandem hydrosilylation of **328a**

4.2.3 Mechanistic Studies

As with the molybdenum-catalysed reduction of arylidene MA derivatives, deuterium labelling studies were carried out to gain insight into the reaction mechanism. Deuterium was used as a nucleophile and an electrophile in the form of trideuteriophenylsilane[22] and deuterium oxide.

Reduction of **367a** with trideuteriophenylsilane followed by hydrolysis with water proceeded smoothly with the product isolated in 85% yield. ^{1}H NMR analysis showed no aldehyde peak at 9.80 ppm (Figure 16) and a singlet at 9.75 ppm was observed in the ^{2}H NMR (Figure 15), no other peaks were observed in the ^{2}H NMR. Furthermore, a triplet at 201.9 ppm was observed in the ^{13}C NMR and bands at 2079 cm^{-1} (C-D) and 1712 cm^{-1} (C=O) were observed in the IR spectra confirming the formation of a deuteroaldehyde. The ^{1}H NMR also showed a 2H triplets at 2.91 ppm and 2.74 (J = 7.5 Hz); a 2H multiplet is observed at 2.77-2.72 ppm in the ^{1}H NMR spectra of **268a** (Figure 17). This analysis suggests the formation of the deuterioaldehyde **412a** (Scheme 153), this was confirmed by ^{1}H-, ^{2}D-, and ^{13}C NMR, mass spectrometry and IR analysis.



Scheme 153 Reduction of **367a** using trideuterophenylsilane

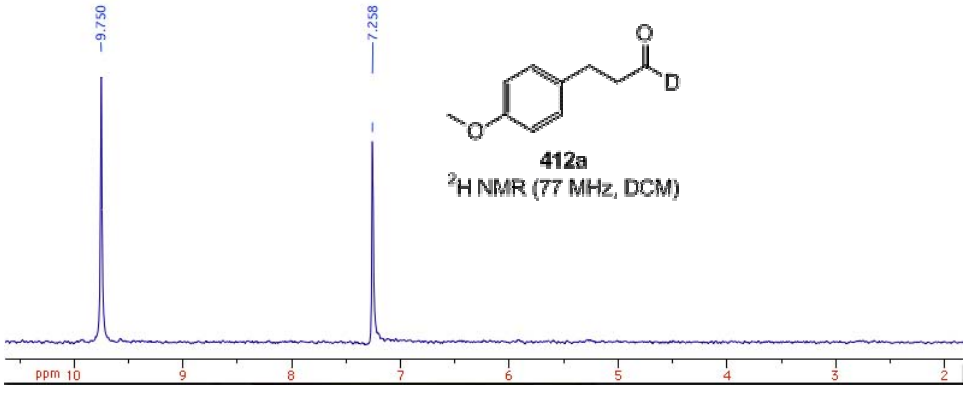


Figure 15 ^{2}D NMR of 1-deutero-3-(4-methoxyphenyl)propanal **412a**

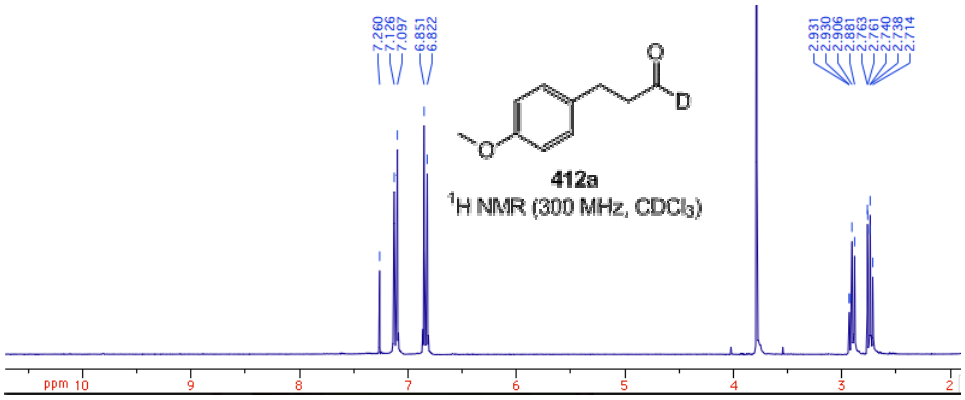


Figure 16 ^{1}H NMR of 1-deutero-3-(4-methoxyphenyl)propanal **412a**

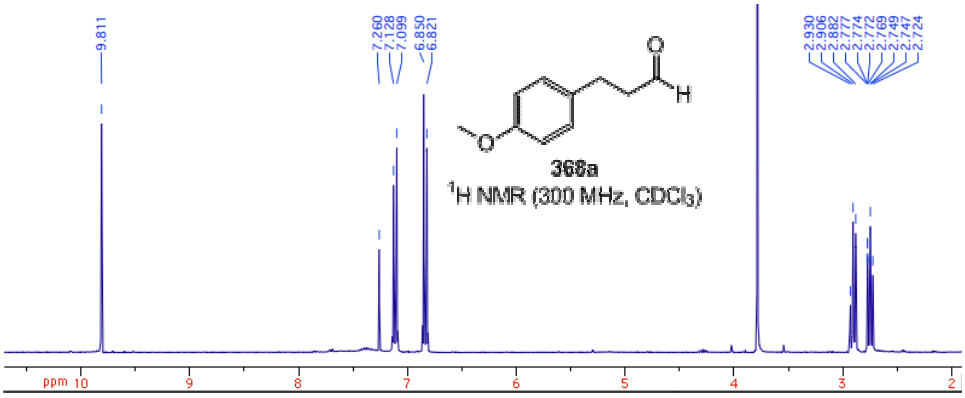
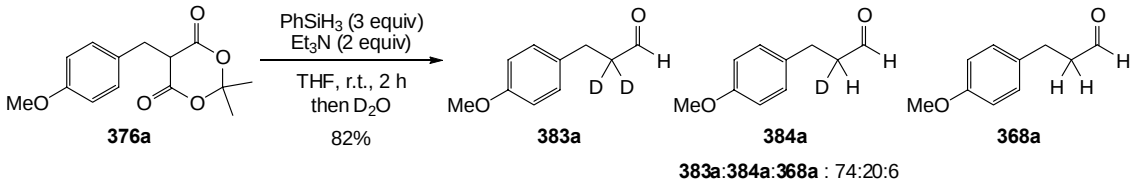


Figure 17 ^{1}H NMR of 3-(4-methoxyphenyl)propanal **368a**

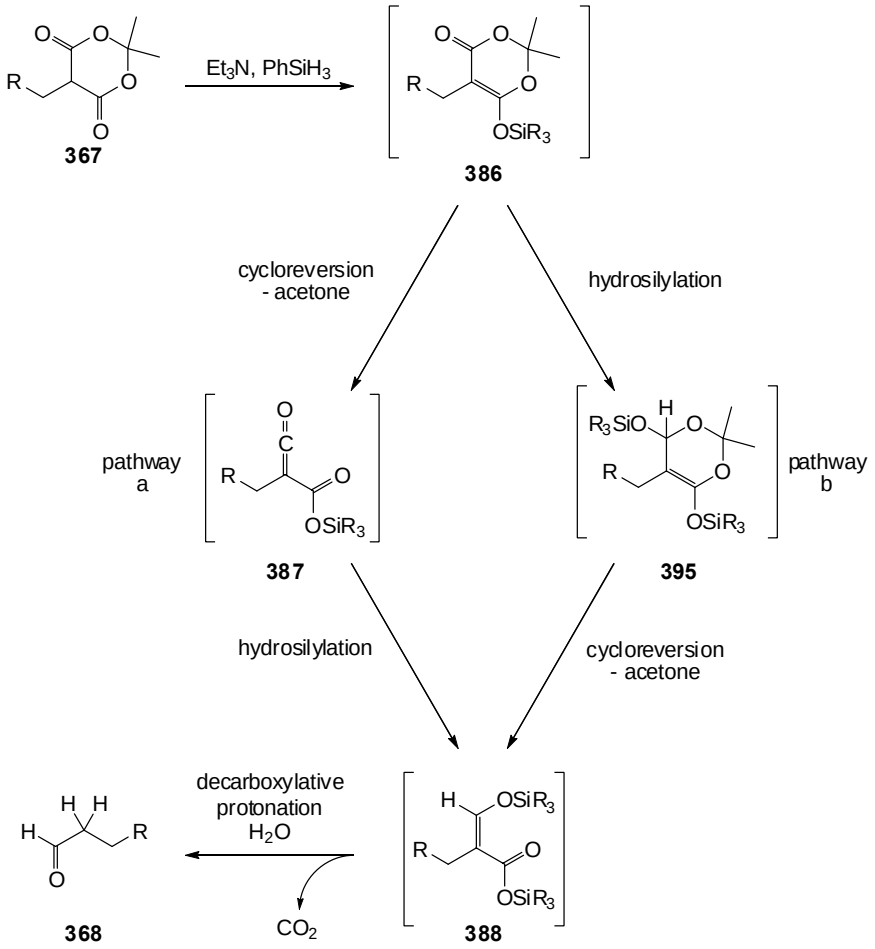
Reduction of **367a** with phenylsilane, followed by hydrolysis with deuterium oxide gave the same mixture of products as the molybdenum-catalysed reduction of alkylidene MA derivative **328a** hydrolysed with deuterium oxide (*cf.* 3.3.6.1). Again incomplete deuteration at the α-carbon occurred, however, the α,α'-dideuterated product **383a** was the major product of the reaction.



Scheme 154 Reduction of **367a** quenched by deuterium oxide

4.2.4 Proposed Mechanism

There are two possible reaction pathways for the amine promoted reduction of 5-monoalkyl Meldrum's acid derivatives. Both proposed pathways are initiated by the deprotonation of **367** on addition of triethylamine and subsequent silylation by phenylsilane to give **386** (Scheme 155). In pathway a the cycloreversion of **386** gives α-oxoketene **387** which undergoes hydrosilylation to intermediate **388** and this remains in solution until decarboxylative protonation at the end of the reaction (decarboxylation confirmed by limewater test). In pathway b the ester moiety of **386** is hydrosilylated to give **395**; this then undergoes cycloreversion to give, like pathway a, **388**.



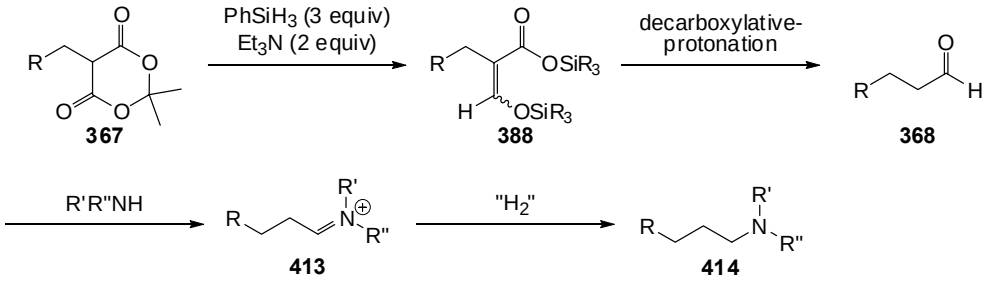
Scheme 155 Proposed reaction pathways for the triethylamine promoted reduction of 5-monoalkyl MAs

Attempts to isolate intermediate **388** were unsucceful. However, ^{1}NMR analysis of the reaction mixture prior to protonation showed loss of acetone is occurring prior to decarboxylative protonation.

4.3 Application of Aldehyde Synthesis in Multi-Step Syntheses

Multiple-step syntheses carried out in one pot are of interest as they can increase efficiency by avoiding repeated isolation and purification processes. It was envisaged that the mild, expeditious synthesis of β-substituted propionaldehydes, described above, could be used as the first step in a one-pot multi-step synthesis due to the synthetic utility of the newly formed aldehyde functionality.

To explore the synthetic utility of the amine promoted β-substituted propionaldehyde synthesis, a one-pot malonate reduction/reductive amination was proposed to access γ-substituted propylamines **414** directly from 5-monoalkyl Meldrum's acid derivatives (Scheme 156). Decarboxylative protonation would reveal the protected aldehyde functionality; this would undergo imine formation on addition of a primary or secondary amine. Reduction of the imine would result in the formation of the desired γ-substituted propylamines.



Scheme 156 Envisaged process for γ-substituted propylamine synthesis from **367**

Methanol proved to be a suitable proton source giving the aldehyde before imine formation on addition of a suitable amine. Imine reduction was, as expected, achieved with both Pd/C with 1 atmosphere of molecular hydrogen[23] and $NaBH(OAc)_3$[24] (Table 13, entries 1 and 2). Higher yields were observed with the palladium-catalysed hydrogenation.

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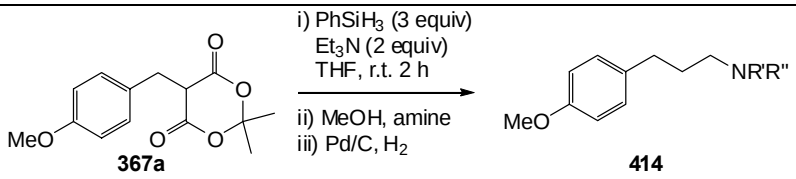
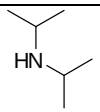
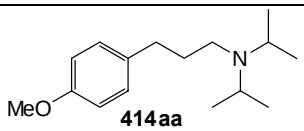
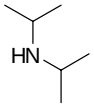
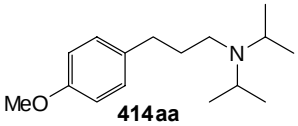
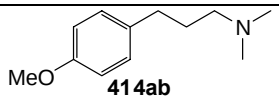
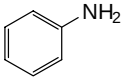
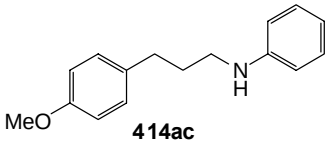
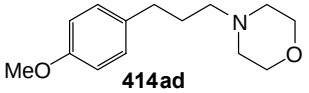
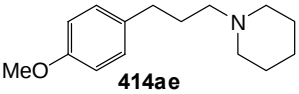
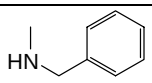
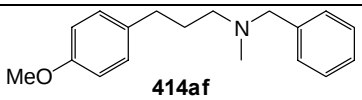
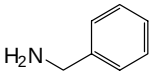
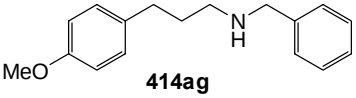
Table 13 One-pot reduction/reductive amination of **367a**



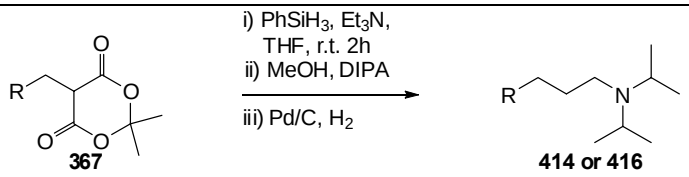
entry	amine	product[a]	yield, %[b]
1	 **415a**	 **414aa**	63
2	 **415a**	 **414aa**	31[c]
3	 **415b**	 **414ab**	52
4	 **415c**	 **414ac**	48
5	 **415d**	 **414ad**	41
6	 **415e**	 **414ae**	50
7	 **415f**	 **414af**	52
8	 **415g**	 **414ag**	37

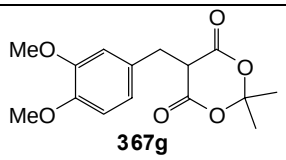
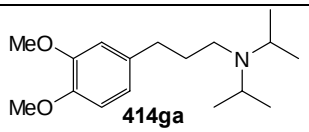
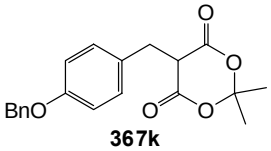
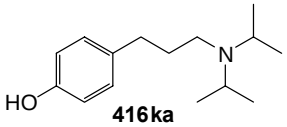
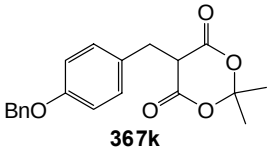
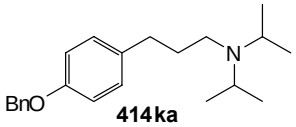
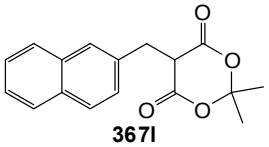
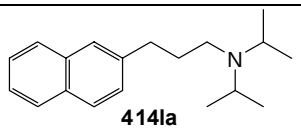
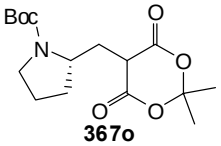
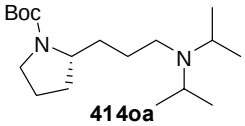
[a] Reaction conditions : (i) Substrate **367a** (1 equiv), phenylsilane (3 equiv), triethylamine (2 equiv), THF, r.t., 2 h, (ii) methanol, amine (2 equiv), r.t. 1 h, (iii) Pd/C, $H_{2\ (g)}$ (1 atm), r.t. 16 h. [b] Isolated yields.
[c] $NaBH(OAc)_3$ (2 equiv) used.

This one-pot process was carried out with a range of primary and secondary amines and alkylidene MA derivative **367a**, products were isolated in moderate yields (Table 13).

Despite high steric hindrance, diisopropylamine gave the highest yield of 63%, a pleasing yield for this multi-step process (entry 1). Yields varied little for other secondary amines (entries 3, 6 and 7) with the exception of the less nucleophilic morpholine **415d** (entry 5). A poor yield was observed with the use of benzylamine **415g** (entry 8); it is likely that this is a consequence of the dialkylation of the amine. Aniline **415c** gives the reductive amination product in 48% yield (entry 4)

Table 14 One-pot reduction/reductive amination of 5-monoalkyl MAs



entry	substrate	product[a]	yield, %[b]
1	 **367g**	 **414ga**	56
2	 **367k**	 **416ka**	57
3	 **367k**	 **414ka**	32[c]
4	 **367l**	 **414la**	41
5	 **367o**	 **414oa**	61

[a] Reaction conditions : (i) Substrate **367** (1 equiv), phenylsilane (3 equiv), triethylamine (2 equiv), THF, r.t., 2 h, (ii) methanol, diisopropylamine (2 equiv), r.t. 1 h, (iii) Pd/C, $H_{2\ (g)}$ (1 atm), r.t. 16 h. [b] Isolated yields. [c] $NaBH(OAc)_3$ (2 equiv) used.

This one-pot process tolerated a range of 5-monoalkyl MA derivatives (Table 14). Of note is the synthesis of **416ka** and **414ka** from the common substrate **367k**, by adjusting the reductive conditions the benzyl protecting group can be either removed or left unchanged (entries 2 and 3, Table 14). The trend in reactivity for this multi-step process is the same as the synthesis of β-substituted propionaldehydes with the exception of **414la** which was isolated in a poor 41% yield (entry 4).

4.4 Conclusion

A triethylamine promoted reduction of 5-monoalkyl MA derivatives to β-substituted aldehydes by phenylsilane has been reported. Good yields have been observed with a range of substrates using these mild, expeditious reductive conditions. Evidence towards a proposed mechanism has been acquired through deuterium labelling studies and a limewater test.

This reductive system has been used in a one-pot reductive aldehyde formation/reductive amination for the synthesis of γ-substituted propylamines directly from 5-monoalkyl MA derivatives. Moderate yields were observed for this one-pot process.

Under more forcing conditions it was possible to access β-aryl aldehydes directly from alkylidene MA derivatives; an amine promoted conjugate reduction is the initiating step of this reaction.

4.5 References

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Chapter 5 - Experimental

5.1 General Information

Commercially available solvents and reagents were obtained from Sigma Aldrich Company Ltd, Lancaster Synthesis Ltd, Fisher Scientific Ltd and Strem Chemicals UK and were used without further purification. Solvents and were deoxygenated where necessary by purging with nitrogen. 'Petrol' refers to the fraction of petroleum ether boiling in the range of 40-60 ^{o}C. For catalytic experiments, HPLC-grade solvent was passed through an Innovative Technology Pure-Solv solvent purification system. Microwave reactions were performed using a CEM Discover 300W laboratory microwave instrument.

NMR spectra were recorded on Bruker AV 250, AV300 or AV 500 spectrometers at 298 K unless otherwise stated. Chemical shifts (δ) are expressed in parts per million (ppm). ^{1}H NMR spectra were referenced internally to residual protio-solvent (C*H*Cl$_3$ at 7.26 ppm), ^{13}C NMR spectra were referenced to deuterio-solvent resonance (*C*DCl$_3$ at 77.0 ppm) and ^{2}H NMR were referenced to deuterio-solvent (C*D*Cl$_3$ at 7.26 ppm). Assignments were supported by ^{13}C PENDANT NMR and homo- and heteronuclear, one- and two-dimensional experiments as appropriate. The multiplicities of the spectroscopic data are presented in the following manner: singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), double of doublet of doublets (ddd), doublet of doublet of triplets (ddt), triplet (t), triplet of doublets (td), quartet (q), quintet (quin), septet (sept) and multiplet (m). Coupling constants (*J*) are expressed in Hertz (Hz), The assignment of aromatic proton resonances for *para* disubstituted benzene rings has been simplified by assuming an AB system, however, the characteristic features of an AA'BB'system were observed in the NMR spectra.

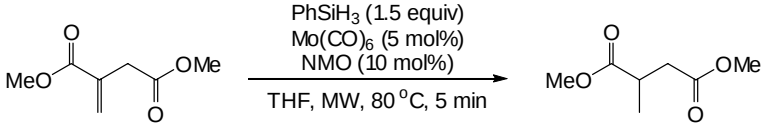
IR spectra were recorded on either a Nicolet-Nexus FTIR spectrometer, over the range 4000-600 cm^{-1} and averaged over 32 scans, using KBr discs or NaCl plates. Melting points were determined using a Buchi 535 melting point apparatus and are uncorrected. Electrospray Ionisation (ESI) and Electron Impact (EI) mass spectra were obtained at the

EPSRC National Mass Spectrometry Service Centre at Swansea University or on a Bruker MicroTOF spectrometer at the mass spectrometry service at the University of Bath.

High Performance Liquid Chromatography (HPLC) was performed on an Agilent 1100 Series system, using a Chiralpak OJ column by Daicel Chemical Industries Ltd. Elemental analyses were recorded on a Micromass Autospec Spectrometer at the University of Bath.

5.2 Molybdenum-Catalysed Conjugate Reduction

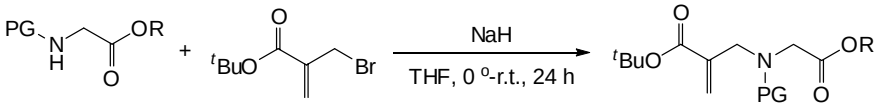
5.2.1: Dimethyl 2-methylsuccinate 230



An oven dried microwave vial was charged with a solution dimethyl itaconate (79.1 mg, 0.5 mmol), molybdenum hexacarbonyl (6.6 mg, 0.025 mmol, 5 mol%) and *N*-methylmorpholine *N*-oxide monohydrate (5.9 mg, 0.044 mmol, 9 mol%) in tetrahydrofuran (1.0 mL). Phenylsilane (92 μL, 0.75 mmol) was added to the solution and the vial was sealed under an atmosphere of nitrogen. The solution was heated to 80 ^{o}C (100 W) in a microwave reactor for 5 minutes and allowed to cool to room temperature. After cooling to room temperature, water (0.5 mL) was added to the reaction mixture and the resulting solution was stirred at ambient temperature for 15 minutes. The solution was diluted with diethyl ether (25 mL) and washed with water (2 x 25 mL) followed by saturated brine (25 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. Methanol (20 mL) was added to the residue, the solution was filtered through celite and concentrated *in vacuo* to afford the desired compound as a colourless oil (147.4 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (3H, s, OC*H*$_3$), 3.68 (3H, s, OC*H*$_3$), 3.00-2.89 (1H, m, MeO$_2$CC*H*), 2.74 (1H, dd, J^1 = 16.2 Hz, J^2 = 8.3 Hz, C*H*$_2$CO$_2$Me), 2.41 (1H, dd, J^1 = 16.2 Hz, J^2 = 6.0 Hz, C*H*$_2$CO$_2$Me), 1.22 (3H, d, J = 7.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.1, 172.7, 52.5, 52.4, 37.9, 36.0, 17.4; HRMS (ESI) calcd for $C_7H_{12}NaO_4$ $[M+Na]^+$: *m*/*z* 183.0628, found 183.0623. Data identical to literature values.[1]

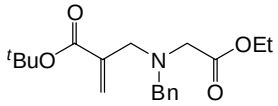
5.3 Synthesis of α-Substituted Acrylic Esters

5.3.1: General Procedure for the Synthesis of α-Substituted Acrylic Esters



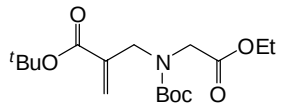
N-Protected gylcine methyl or ethyl ester **254** was added to a stirred solution of sodium hydride (60% dispersion in mineral oil) in tetrahydrofuran at 0 ^{o}C. The subsequent solution was stirred for 1 hour at 0 ^{o}C. *tert*-Butyl 2-(bromomethyl)acrylate **255** was then added to the reaction mixture and the resulting solution was stirred at ambient temperature for 24 hours. The reaction mixture was quenched with water and dissolved in diethyl ether. The organic phase was washed with water and saturated brine. The organic phase was extracted, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography.

5.3.2: *tert*-butyl 2-((benzyl(2-ethoxy-2-oxoethyl)amino)methyl)acrylate 222



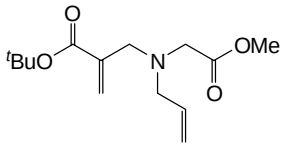
N-Benzyl glycine ethyl ester **254a** (1.93 g, 10.0 mmol), sodium hydride (0.48 g, 12.0 mmol), *tert*-butyl 2-(bromomethyl)acrylate **255** (2.42 g, 11.0 mmol) and tetrahydrofuran (50 mL) were reacted under the standard protocol and purified by flash column chromatography (9:1 petrol:ethyl acetate) to give the desired compound as a colourless oil (2.15 g, 64%); R_f (9:1 petrol:ethyl acetate) 0.24; IR (neat, cm^{-1}) *v* 2978, 2932 (C-H), 1736, 1711 (C=O), 1636 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.17 (5H, m, Ar-*H*), 6.13 (1H, s, C=CH_2), 5.76 (1H, s, C=CH_2), 4.11 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 3.80 (2H, s, NCH_2Ph), 3.50 (2H, s, NCH_2C=C), 3.28 (2H, s, NCH_2CO$_2$Et), 1.46 (9H, s, C(CH_3)$_3$), 1.22 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.9, 166.7, 139.9, 139.4, 129.2, 128.7, 127.5, 125.7, 81.0, 60.6, 57.8, 55.0, 53.9, 28.5, 14.7; HRMS (ESI) calcd for $C_{19}H_{27}NNaO_4$ $[M+Na]^+$: *m*/*z* 356.1838, found 356.1833; Anal. calcd for $C_{19}H_{27}NO_4$: C 68.4, H 8.16, N 4.20, found: C 68.5, H 8.27, N 4.25.

5.3.3: *tert*-butyl 2-((*tert*-butoxycarbonyl(2-ethoxy-2-oxoethyl)amino)methyl)acrylate 256



N-Boc glycine ethyl ester **254b** (2.25 g, 15 mmol), sodium hydride (0.72 g, 18 mmol), *tert*-butyl 2-(bromomethyl)acetate **255** (3.63 g, 16.5 mmol) and tetrahydrofuran (75 mL) were reacted under standard conditions and purified by flash column chromatography (9:1 petrol:ethyl acetate) to give the desired compound, a colourless oil, as a 1:1 mixture of rotamers (4.11 g, 80%); R_f (9:1 petrol:ethyl acetate) 0.27; IR (neat, cm^{-1}) ν 2980, 2935 (C-H), 1753, 1706 (C=O), 1638 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 and 617 (1H, s, C=CH_2), 5.67 and 5.60 (1H, s, C=CH_2), 4.17 and 4.16 (2H, q, J = 7.2 Hz, OCH_2CH$_3$), 4.11 and 4.06 (2H, s, NCH_2C=C), 3.99 and 3.88 (2H, s, NCH_2CO$_2$Et), 1.48 and 1.47 (9H, s, C(CH_3)$_3$), 1.44 and 1.42 (9H, s, C(CH_3)$_3$), 1.26 and 1.25 (3H, t, J = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.4 and 170.3, 165.9, 156.2 and 155.5, 138.4 and 138.1, 126.1 and 125.3, 81.6 and 81.4, 80.9 and 80.8, 61.3, 50.0 and 49.5, 49.3 and 49.2, 28.7 and 28.6, 28.4, 14.6 and 14.5; HRMS (ESI) calcd for $C_{17}H_{30}NO_6$ $[M+H]^+$: m/z 344.2073, found 344.2063.

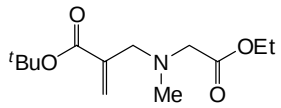
5.3.4: *tert*-butyl 2-((allyl(2-methoxy-2-oxoethyl)amino)methyl)acrylate 257



N-Allyl glycine methyl ester **254c** (1.29 g, 10 mmol), sodium hydride (0.48 g, 12.0 mmol), *tert*-butyl 2-(bromomethyl)acetate **255** (2.42 g, 11.0 mmol) and tetrahydrofuran (50 mL) were reacted under standard conditions and purified by flash column chromatography (9:1 petrol:ethyl acetate) to give the desired compound as a colourless oil (1.43 g, 53%); R_f (9:1 petrol:ethyl acetate) 0.22; IR (neat, cm^{-1}) ν 2979, 2954, 2941, 2845 (C-H), 1741, 1715 (C=O), 1641 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (1H, s, C=CH_2), 5.81 (1H, ddt, J^1 = 17.3 Hz, J^2 = 10.2 Hz, J^3 = 6.4 Hz, NCH$_2$CHCH$_2$), 5.71 (1H, s, C=CH_2), 5.18 (1H, ddt, J^1 = 17.3 Hz, J^2 = 1.9 Hz, J^3 = 1.5 Hz, NCH$_2$CHCH_2), 5.13 (1H, ddt, J^1 = 10.2 Hz, J^2 = 1.9 Hz, J^3 = 1.1 Hz, NCH$_2$CHCH_2), 3.67 (3H, s, CO$_2$CH_3), 3.44 (2H, s, NCH_2C=C), 3.35 (2H, s, NCH_2CO$_2$Me), 3.26 (2H, ddd, J^1 = 6.4 Hz, J^2 = 1.5 Hz, J^3 = 1.1 Hz, NCH_2CHCH$_2$), 1.48

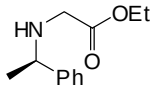
(9H, s, C(CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.4, 166.6, 139.7, 136.0, 125.9, 118.1, 81.1, 57.3, 54.6, 54.11, 51.7, 28.5; HRMS (ESI) calcd for $C_{14}H_{23}NNaO_4$ $[M+Na]^+$: *m*/*z* 292.1525, found 292.1519.

5.3.5: *tert*-butyl 2-(((2-ethoxy-2-oxoethyl)methylamino)methyl)acrylate 218



Sarcosine ethyl ester hydrochloride **254d** (694 mg, 4.53 mmol), sodium hydride (422 mg, 10.5 mmol), *tert*-butyl 2-(bromomethyl)acetate **255** (1 g, 4.53 mmol) and tetrahydrofuran (50 mL) were reacted under standard conditions and purified by flash column chromatography (4:1 petrol:ethyl acetate) to give the desired compound as a colourless oil (932 mg, 80%); R_f (4:1 petrol:ethyl acetate) 0.27; IR (neat, cm^{-1}) *v* 2980 (C-H), 1740, 1713 (C=O), 1636 (C=C); ^{1}H (300 MHz, $CDCl_3$) δ 6.08 (1H, s, C=C*H*H), 5.61 (1H, s, C=CH*H*), 4.07 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 3.28 (2H, s, NCH_2C=C), 3.20 (2H, s, CH_2CO$_2$Et), 2.30 (3H, s, NCH_3), 1.40 (9H, s, C(CH_3)$_3$), 1.18 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.3, 166.4, 139.2, 126.0, 80.9, 60.5, 58.1, 57.1, 42.3, 28.3, 14.6; HRMS (ESI) calcd for $C_{13}H_{23}NNaO_4$ $[M+Na]^+$: *m*/*z* 280.1524, found 280.1522.

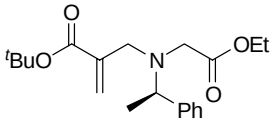
5.3.6: (*R*)-ethyl 2-(1-phenylethylamino)acetate 274



(*R*)-1-Phenylethylamine **272** (1.05 mL, 8.25 mmol) was added to a stirred solution of sodium hydride (60% dispersion in mineral oil) (330 mg, 8.25 mmol) in tetrahydrofuran (25 mL) at 0 ^{o}C. The subsequent solution was stirred for 1 hour at 0 ^{o}C. Ethyl 2-bromoacetate **273** (457 μL, 4.13 mmol) was then added to the reaction mixture and the resulting solution was stirred at ambient temperature for 24 hours. The reaction mixture was quenched with water and dissolved in diethyl ether (50 mL). The organic phase was washed with water (50 mL) and saturated brine (50 mL). The organic phase was extracted, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (4:1 petrol:ethylacetate) to give the desired compound as a colourless oil (746 mg, 87%); R_f (4:1 petrol:ethyl acetate) 0.20; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (5H, m, Ar*H*), 4.13 (2H, q, *J* = 7.2 Hz, CO$_2$CH_2CH$_3$), 3.77 (1H, q, *J* = 6.4 Hz, NC*H*), 3.27 (1H, d, *J* = 17.3 Hz,

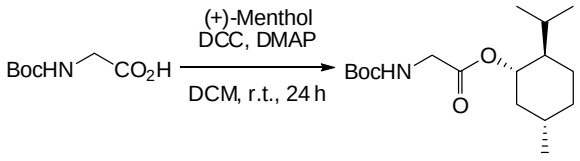
NCH_2CO$_2$Et), 3.19 (1H, d, J = 17.3 Hz, NCH_2CO$_2$Et), 1.90 (1H, s, NH), 1.36 (3H, d, J = 6.4 Hz, NCHCH_3), 1.22 (3H, t, J = 7.2 Hz, CO$_2$CH$_2$CH_3); ^{13}C (75.5 MHz, CDCl$_3$) δ 173.0, 145.0, 128.9, 127.6, 127.2, 61.1, 58.1, 49.3, 24.6, 14.6; HRMS (ESI) calcd for $C_{12}H_{17}NnaO_2$ [M+Na]$^+$: m/z 230.1152, found 230.1142. Data identical to literature values.[2]

5.3.7: (*R*)-*tert*-butyl 2-(((2-ethoxy-2-oxoethyl)(1-phenylethyl)amino)methyl)acrylate 275



2-((*R*)-1-Phenylethylamino)acetate **274** (711 mg, 3.43 mmol), sodium hydroxide (137 mg, 3.43 mmol), *tert*-butyl 2-(bromomethyl)acetate **255** (663 mg, 3.43 mmol) and tetrahydrofuran (20 mL) were reacted under standard conditions and purified by flash column chromatography (10:1 petrol:ethyl acetate) to give the desired compound as a colourless oil (544 mg, 46%); R_f (10:1 petrol:ethyl acetate) 0.24; $[\alpha]_D^{24}$ -1.3 (c = 0.8, CDCl$_3$); IR (neat, cm^{-1}) v 2980, 2935 (C-H), 1735, 1708 (C=O), 1639 (C=C); ^{1}H NMR (300 MHz, CHCl$_3$) δ 7.40-7.19 (5H, m, Ar), 6.13 (1H, s, C=CHH), 5.87 (1H, s, C=CHH), 4.12 (2H, q, J = 7.2 Hz, OCH_2CH$_3$), 4.10 (1H, q, J = 6.8 Hz, NCH), 3.49 (1H, d, J = 16.2 Hz, NCH_2C=C), 3.45 (1H, d, J = 16.2 Hz, NCH_2C=C), 3.40 (1H, d, J = 17.3 Hz, NCH_2CO$_2$Et), 3.25 (1H, d, J = 17.3 Hz, NCH_2CO$_2$Et), 1.48 (9H, s, C(CH_3)$_3$), 1.36 (3H, d, J = 6.8 Hz, CHCH_3), 1.24 (3H, t, 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 172.5, 166.7, 144.7, 140.4, 128.6, 127.9, 127.3, 125.4, 81.0, 60.7, 60.6, 52.1, 51.8, 28.5, 19.3, 14.6; HRMS (ESI) calcd for $C_{20}H_{29}NO_4Na$ [M+Na]$^+$: m/z 370.1994, found 370.1994.

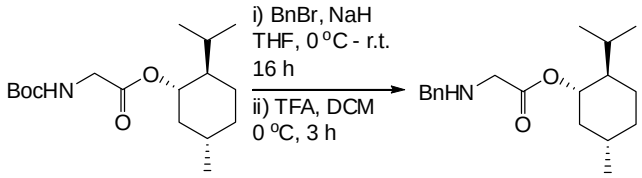
5.3.8: (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-(*tert*-butoxycarbonylamino)acetate 290



To a stirred solution of *N*-Boc glycine **289** (3.50 g, 20.2 mmol) in dichloromethane (110 mL) was added dicyclohexylcarbodiimide (4.18 g, 20.2 mmol), and dimethylaminopyridine (110 mg, 0.9 mmol) at 0 ^{o}C. The resulting solution was stirred for 1 hour before the addition of (+)-menthol (3.78 g, 24.2 mmol) and then stirred for a further 24 hours after

reaching ambient temperature. The reaction mixture was dissolved in DCM (100 mL) and washed with water (200 mL) and saturated brine (200 mL); the organic phase was extracted and concentrated *in vacuo*. The residue was dissolved in ethyl acetate and filtered through celite, the filtrate was concentrated *in vacuo* and purified by flash column chromatography (12:1 petrol:diethyl ether) to give the desired product as a colourless oil (5.09 g, 80%); R_f (12:1 petrol:diethyl ether) 0.21; $[\alpha]_D^{24}$ +75.3 (c = 0.9, $CHCl_3$); IR (neat, cm^{-1}) ν IR 3034 (N-H), 2958, 2871 (C-H), 1740, 1701 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.02 (1H, br s, N*H*), 4.74 (1H, td, J^1 = 10.9 Hz, J^2 = 4.5 Hz, OC*H*), 3.87 (2H, d, J = 5.3 Hz, NCH_2), 2.01-1.94 (1H, m, *mentholate*), 1.90-1.75 (1H, m, *mentholate*), 1.73-1.63 (2H, m, *mentholate*), 1.53-1.32 (2H, m, *mentholate*), 1.44 (9H, s, C(CH_3)$_3$), 1.11-0.79 (3H, m, *mentholate*), 0.89 (3H, d, J = 6.5 Hz, CHC(CH_3)$_2$), 0.87 (3H, d, J = 6.5 Hz, CHC(CH_3)$_2$), 0.74 (3H, d, J = 6.8 Hz, CHCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.3, 156.0, 80.2, 75.8, 47.3, 43.0, 41.2, 34.5, 31.8, 28.7, 26.6, 23.8, 22.4, 21.1, 16.7; HRMS (ESI) calcd for $C_{17}H_{32}NO_4$ $[M+H]^+$: *m*/*z* 314.2331, found 314.2330.

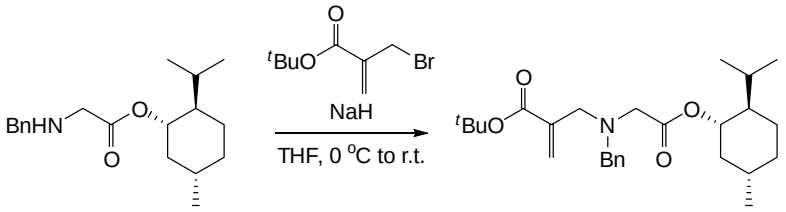
5.3.9: (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-(benzylamino)acetate 291



(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl 2-(*tert*-butoxycarbonylamino)acetate **289** (3.0 g, 9.57 mmol) was added to a stirred solution of sodium hydride (60% dispersion in mineral oil) (460 mg, 11.48 mmol) in tetrahydrofuran (100 mL) at 0 °C. The resulting solution was stirred at 0 °C for 1 hour then benzyl bromide (1.71 mL, 14.36 mmol) was added and the solution stirred at ambient temperature for 24 hours. The reaction mixture was dissolved in diethyl ether (100 mL) and washed with saturated sodium hydrogen carbonate solution (2 x 150 mL), water (150 mL) and saturated brine (150 mL). The organic phase was extracted and concentrated *in vacuo* and the residue was reacted further without isolation of the product. The residue was dissolved in dichloromethane (30 mL) and stirred at 0 °C. Trifluoacetic acid (7.5 mL) added to the solution drop wise, the reaction mixture was then stirred at ambient temperature for 3 hours. The reaction mixture was concentrated *in vacuo* and the residue dissolved in diethyl ether (100 mL). The organic phase was washed with saturated sodium hydrogen carbonate solution (3 x 100 mL), water (100 mL) and brine

(100 mL). The organic phase was extracted, concentrated *in vacuo* and purified by flash column chromatography (10:1 petrol:ethyl acetate) to give the desired compound as a colourless oil (1.34 g, 46%); R_f (10:1 petrol:ethyl acetate) 0.28; $[\alpha]_D^{24}$ +34.6 (c = 7.5, $CHCl_3$); IR (neat, cm^{-1}) ν 3030 (N-H), 2957, 2870 (C-H), 1732 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.19 (5H, m, Ar), 4.74 (1H, td, J^1 = 10.9 Hz, J^2 = 4.5 Hz, OC*H*), 3.77 (2H, s, NCH_2Ph), 3.35 (2H, s, NC$H_2CO_2X_c$), 2.01-1.96 (1H, m, *mentholate*), 1.91 (1H, br s, N*H*), 1.87-1.74 (1H, m, *mentholate*), 1.70-1.61 (2H, m, *mentholate*), 1.39-1.29 (1H, m, *mentholate*), 1.11-0.80 (4H, m, *mentholate*), 0.88 (3H, d, J = 6.5 Hz, CH(CH_3)$_2$), 0.86 (3H, d, (J = 6.5 Hz, CH(CH_3)$_2$), 0.75 (3H, d, J = 7.2 Hz, CHCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.4, 140.0, 128.8, 128.7, 127.5, 75.1, 53.7, 50.7, 47.4, 41.4, 34.6, 31.8, 26.7, 23.8, 22.4, 21.1, 16.7; HRMS (ESI) calcd for $C_{19}H_{30}NO_2$ $[M+H]^+$: *m*/*z* 304.2277, found 304.2270.

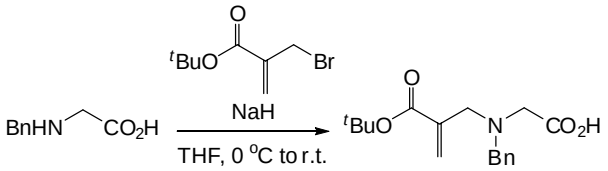
5.3.10: *tert*-butyl 2-((benzyl(2-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl)acrylate 292



(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl 2-(benzylamino)acetate **291** (500 mg, 1.65 mmol) was added to a solution of sodium hydride (60% dispersion in mineral oil) (72.5 mg, 1.81 mmol) in tetrahydrofuran (20 mL) at 0 ^{o}C. The subsequent solution was stirred for at 0 ^{o}C for 1 hour before the addition of *tert*-butyl 2-(bromomethyl)acrylate **255** (750 mg, 1.81 mmol). The reaction mixture was stirred at ambient temperature for 24 hours. The reaction mixture was dissolved in diethyl ether (50 mL) and washed with saturated sodium hydrogen carbonate solution (2 x 50 mL), water (50 mL) and brine (50 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The mixture was purified by flash column chromatography (15:1 petrol:diethyl ether) to give the desired product as a colourless oil (185 mg, 66% yield); R_f (15:1 petrol:diethyl ether) 0.25; $[\alpha]_D^{24}$ +56.1 (c = 1.8, $CHCl_3$); IR (neat, cm^{-1}) ν 2957, 2870 (C-H), 1738, 1712 (C=O), 1637 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.23 (5H, m, Ar), 6.19 (1H, d, J = 6.19 Hz, C=C*H*H), 5.81 (1H, d, J = 1.9 Hz, C=CH*H*), 4.78 (1H, td, J^1 = 10.9 Hz, J^2 = 4.5 Hz, OC*H*), 3.87 (2H, s, NCH_2Ph), 3.58 (2H, s, NCH_2C=C), 3.32 (2H, s, NC$H_2CO_2X_c$), 2.07-2.00 (1H,

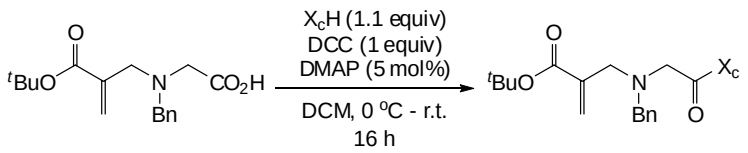
m, *mentholate*), 1.94-1.79 (1H, m, *mentholate*), 1.74-1.67 (2H, m, *mentholate*), 1.61-1.47 (1H, m, *mentholate*), 1.53 (9H, s, C(CH_3)$_3$), 1.44-1.34 (1H, m, *mentholate*), 1.17-0.88 (3H, m, *mentholate*), 0.94 (3H, d, J = 6.5 Hz, CH(CH_3)$_2$), 0.92 (3H, d, J = 6.5 Hz, CH(CH_3)$_2$), 0.81 (3H, d, J = 6.8 Hz, CHCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.0, 165.2, 138.7, 138.0, 127.7, 127.2, 126.0, 124.3, 124.0, 79.5, 73.1, 56.4, 53.7, 52.6, 46.0, 40.0, 33.2, 29.9, 27.1, 25.2, 21.3, 19.7, 15.3; HRMS (ESI) calcd for $C_{27}H_{42}NO_4$ $[M+H]^+$: m/z 444.3114, found 444.3099; Anal. calcd for $C_{27}H_{41}NO_4$: C 73.1, H 9.32, N 3.16, found: C 73.4, H 9.41, N 3.27.

5.3.11: 2-(benzyl(2-(tert-butoxycarbonyl)allyl)amino)acetic acid 295



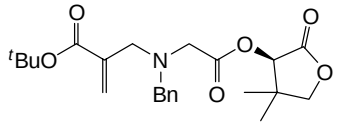
N-Benzylglycine **294** (250 mg, 1.51 mmol) was added to a solution of sodium hydride (60% dispersion in mineral oil) (121 mg, 3.26 mmol) in tetrahydrofuran (15 mL) at 0 °C. The resulting solution was stirred at 0 °C for 1 hour before the addition of *tert*-butyl 2-(bromomethyl)acrylate **255** (266 mg, 1.38 mmol). The reaction mixture was allowed to stir for 24 hours at ambient temperature. The reaction mixture was dissolved in DCM (50 mL) and acidified with 1 M $HCl_{(aq)}$ (10 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (10:1 ethyl acetate:methanol) to give the desired product as a colourless viscous oil (115 mg, 25%); R_f (10:1 ethyl acetate:methanol) 0.15; IR (neat, cm^{-1}) v 3238 (O-H), 2981, 2934 (C-H), 1702 (C=O), 1636 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.40 (1H, br s, CO_2H), 7.35-7.22 (5H, m, Ar), 6.28 (1H, s, C=CHH), 5.79 (1H, s, C=CHH), 3.70 (2H, s, NCH_2C=C), 3.45 (2H, s, NCH_2Ph), 3.25 (2H, s, NCH_2CO$_2$H), 1.54 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.3, 166.4, 137.8, 137.0, 129.9, 129.4, 129.2, 128.3, 82.6, 58.1, 57.7, 55.7, 28.4; HRMS (ESI) calcd for $C_{17}H_{22}NO_4$ $[M-H]^-$: m/z 304.1549, found 304.1535.

5.3.12: General Procedure for the Coupling of Chiral Auxiliaries and 295



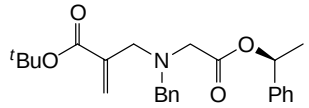
To a stirred solution of 2-(benzyl(2-(tert-butoxycarbonyl)allyl)amino)acetic acid **295** (611 mg, 2 mmol) in dichloromethane (10 mL) was added dicyclohexycarbodiimide (413 mg, 2 mmol) and *N*,*N*-dimethylaminopyridine (12.2 mg, 0.1 mmol, 5 mol%). The resulting solution was stirred at 0 ^{o}C for 1 hour before the addition of alcohol (2.2 mmol). The reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was dissolved in DCM (100 mL) and washed with water (2 x 100 mL) and saturated brine solution (100 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The mixture was purified by flash column chromatography.

5.3.13: (*R*)-*tert*-butyl 2-((benzyl(2-(4,4-dimethyl-2-oxotetrahydrofuran-3-yloxy)-2-oxoethyl)amino)methyl)acrylate 296



(*R*)-Pantolactone **298** (286 mg, 2.2 mmol) was reacted under the general procedure and purified by flash column chromatography (10:1 petrol:ethyl acetate) to give the desired compound as a colourless oil (500 mg, 60%); R_f (10:1 petrol:ethyl acetate) 0.09; $[\alpha]_D^{24}$ +2.0 (c 1.6, $CHCl_3$); IR (neat, cm^{-1}) *v* 2977, 2933 (C-H), 1794, 1756, 1709 (C=O), 1636 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.22 (5H, m, Ar), 6.19 (1H, d, *J* = 1.9 Hz, C=C*H*H), 5.80 (1H, d, *J* = 1.9 Hz, C=CH*H*), 5.41 (1H, s, OC*H*), 4.05 (2H, s, NCH_2COX$_c$), 3.88 (2H, s, NCH_2Ph), 3.59 (2H, s, NCH_2C=C), 3.54 (1H, d, *J* = 17.3 Hz, OCH_2C$(CH_3)_2$), 3.46 (1H, d, *J* = 17.3 Hz, OCH_2C$(CH_3)_2$), 1.52 (9H, s, C$(CH_3)_3$), 1.23 (3H, s, C$(CH_3)_2$), 1.10 (3H, s, C$(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.1, 169.2, 165.2, 138.4, 137.6, 127.8, 127.3, 126.2, 124.4, 79.7, 75.2, 73.9, 56.3, 53.6, 52.0, 39.1, 27.1, 22.0, 19.0; HRMS (ESI) calcd for $C_{23}H_{31}NNaO_6$ [M+Na] : *m*/*z* 440.2049, found 440.2044.

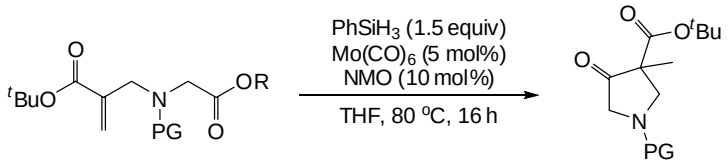
5.3.14: (*S*)-*tert*-butyl 2-((benzyl(2-oxo-2-(1-phenylethoxy)ethyl)amino)methyl)acrylate 297



(*S*)-1-Phenylethanol **299** (266 μL, 2.2 mmol) was reacted under the general procedure and purified by flash column chromatography (15:1 petrol:ethyl acetate) to give the desired compound as a colourless oil (398 mg, 49%); R_f (10:1 petrol:ethyl acetate) 0.30; $[\alpha]_D^{24}$ -29.7 (c 1.7, $CHCl_3$); IR (neat, cm^{-1}) ν 2981, 2933 (C-H), 1745, 1711 (C=O), 1636 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.20 (10H, m, Ar), 6.14 (1H, s, C=C*H*H), 5.93 (1H, q, *J* = 6.8 Hz, OC*H*(Ph)Me), 5.75 (1H, s, C=CH*H*), 3.81 (2H, s, NCH_2Ph), 3.53 (2H, s, NCH_2C=C), 3.37 (1H, d, *J* = 17.3 Hz, NCH_2COX$_c$), 3.31 (1H, d, *J* = 17.3 Hz, NCH_2COX$_c$), 1.54 (3H, d, *J* = 6.8 Hz, CHCH_3), 1.49 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.1, 166.7, 142.0, 140.0, 139.4, 129.2, 129.0, 128.6, 128.3, 127.5, 126.5, 125.6, 81.0, 72.7, 57.8, 55.1, 54.1, 28.5, 22.7; HRMS (ESI) calcd for $C_{25}H_{31}NNaO_4$ $[M+Na]^+$: *m*/*z* 432.2151, found 432.2146.

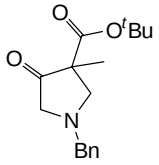
5.4 Molybdenum-Catalysed Reductive Dieckmann Condensation

5.4.1: General Procedure for the Molybdenum-Catalysed Reductive Dieckmann Condensation



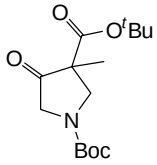
To a solution of molybdenum hexacarbonyl (6.6 mg, 0.025 mmol, 5 mol%) and *N*-methylmorpholine *N*-oxide monohydrate (5.9 mg, 0.044 mmol, 9 mol%) in tetrahydrofuran (3 mL) was added β-substituted acrylate (0.5 mmol) followed by phenylsilane (92 μL, 0.75 mmol). The reaction mixture was stirred at 80 °C for 16 hours. After cooling to room temperature the reaction mixture was dissolved in diethyl ether (25 mL) and washed with water (2 x 25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography.

5.4.2: *tert*-butyl 1-benzyl-3-methyl-4-oxopyrrolidine-3-carboxylate 258



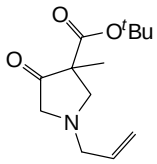
tert-Butyl 2-((benzyl(2-ethoxy-2-oxoethyl)amino)methyl)acrylate **222** (167 mg, 0.5 mmol) was reacted under the general procedure and purified by flash column chromatography (12:1 petrol:diethyl ether) to give the desired product as a colourless oil (128 mg, 88%); R_f (12:1 petrol:diethyl ether) 0.19; IR (neat, cm^{-1}) *v* 2979, 2935, 2797 (C-H), 1766, 1729 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.24 (5H, m, Ar), 3.71 (2H, s, NCH_2Ph), 3.33 (1H, d, *J* = 9.4 Hz, $NCH_2C(Me)CO_2{}^tBu$), 3.20 (1H, d, *J* = 17.0 Hz, $NCH_2C{=}O$), 3.00 (1H, d, *J* = 17.0 Hz, $NCH_2C{=}O$), 2.68 (1H, d, *J* = 9.4 Hz, $NCH_2C(Me)CO_2{}^tBu$), 1.44 (9H, s, $C(CH_3)_3$), 1.35 (3H, s, CH_3); ^{13}C NMR (75.5 Hz, $CDCl_3$) δ 210.9, 170.7, 138.0, 128.9, 128.8, 127.8, 82.4, 62.9, 61.3, 60.3, 58.4, 28.3, 18.2; HRMS (ESI) calcd for $C_{17}H_{23}NNaO_3$ $[M+Na]^+$: *m/z* 312.1576, found 312.1560; Anal. calcd for $C_{17}H_{23}NO_3$: C 70.6, H 8.01, N 4.84, found: C 70.4, H 8.09, N 4.81; Diacel Chiralcel OJ, hexane/propan-2-ol (99:1), 0.5 mL min^{-1}, t_R = 15.3 and 16.6 mins.

5.4.3: di-*tert*-butyl 3-methyl-4-oxopyrrolidine-1,3-dicarboxylate 249



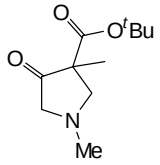
tert-Butyl 2-((*tert*-butoxycarbonyl(2-ethoxy-2-oxoethyl)amino)methyl)acrylate **256** (172 mg, 0.5 mmol) was reacted under the general procedure and purified by flash column chromatography (10:1 petrol:ethyl acetate) to give the desired product, a colourless oil, a 1:1 mixture of rotamers (91.4 mg, 61%); R_f (10:1 petrol:ethyl acetate) 0.28; IR (neat, cm^{-1}) *v* 2977, 2928 (C-H), 1753, 1723, 1699 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 and 4.16 (1H, d, *J* = 12.1 Hz, NC*H*$_2$C(Me)CO$_2$^{t}Bu), 4.03 and 3.98 (1H, d, *J* = 19.2 Hz, NC*H*$_2$C=O), 3.71 (1H, d, *J* = 19.2 Hz, NC*H*$_2$C=O), 3.36 (1H, d, *J* = 12.1 Hz, NC*H*$_2$C(Me)CO$_2$^{t}Bu), 1.45 (9H, s, C(C*H*$_3$)$_3$), 1.40 (9H, s, C(C*H*$_3$)$_3$), 1.30 (3H, s, C*H*$_3$); ^{13}C NMR (75.5 Hz, $CDCl_3$) δ 209.0 and 208.3, 169.5, 154.5, 83.2, 81.0, 57.5 and 56.9, 55.1 and 54.4, 53.1 and 52.6, 28.8, 28.1, 17.7; HRMS (ESI) calcd for $C_{15}H_{25}NNaO_5$ $[M+Na]^+$ *m*/*z* 322.1630, found 322.1632.

5.4.4: *tert*-butyl 1-allyl-3-methyl-4-oxopyrrolidine-3-carboxylate 259



tert-Butyl 2-((allyl(2-methoxy-2-oxoethyl)amino)methyl)acrylate **257** (134.7 mg, 0.5 mmol) was reacted under the general procedure and purified by flash column chromatography (20:1 petrol:ethyl acetate) to give the desired product as a colourless oil (61.0 mg, 51%); R_f (20 petrol:ethyl acetate) 0.26; IR (neat, cm^{-1}) *v* 2983, 2936, 2800 (C-H), 1764, 1725 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (1H, ddt, J^1 = 17.0 Hz, J^2 = 10.2 Hz, J^3 = 6.4 Hz, NCH$_2$C*H*=CH$_2$), 5.23 (1H, dd, J^1 = 17.0 Hz, J^2 = 1.9 Hz, NCH$_2$CH=C*H*$_2$), 5.15 (1H, dd, J^1 = 10.2 Hz, J^2 = 1.9 Hz, NCH$_2$CH=C*H*$_2$), 3.28 (1H, d, *J* = 9.4 Hz, NC*H*$_2$C(Me)CO$_2$^{t}Bu), 3.15 (2H, d, *J* = 6.4 Hz, NC*H*$_2$CH=CH$_2$), 3.12 (1H, d, *J* = 17.0 Hz, NC*H*$_2$C=O), 3.0 (1H, d, *J* = 17.0 Hz, NC*H*$_2$C=O), 2.70 (1H, d, *J* = 9.4 Hz, NC*H*$_2$C(Me)CO$_2$^{t}Bu), 1.42 (9H, s, C(C*H*$_3$)$_3$), 1.33 (3H, s, C*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.0, 170.7, 134.8, 118.1, 82.4, 62.9, 61.2, 59.1, 58.2, 28.2, 18.4; HRMS (ESI) calcd for $C_{13}H_{21}NNaO_3$ [M+Na] : *m*/*z* 262.1419, found 262.1417.

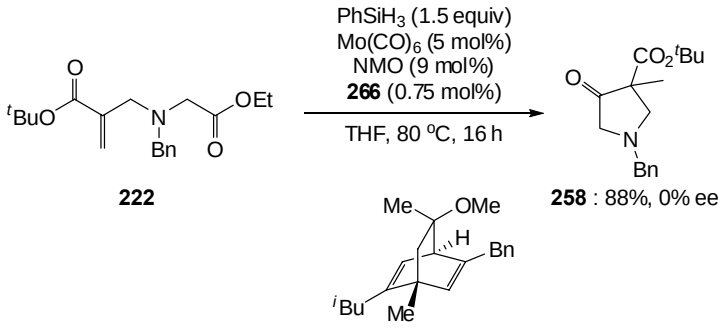
5.4.5: *tert*-butyl 1,3-dimethyl-4-oxopyrrolidine-3-carboxylate 260



tert-Butyl 2-(((2-ethoxy-2-oxoethyl)methylamino)methyl)acrylate **218** (129 mg, 0.5 mmol) was reacted under the general procedure and purified by flash column chromatography (4:1 petrol:ethyl acetate) to give the desired product as a colourless oil (71.8 mg, 67%); R_f (4:1 petrol:ethyl acetate) 0.26; IR (neat, cm^{-1}) ν 2979, 2937, 2783 (C-H), 1766, 1729 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23 (1H, d, J = 9.4 Hz, NCH_2C(Me)C$O_2{}^t$Bu), 3.10 (1H, d, J = 17.0 Hz, NCH_2C=O), 2.99 (1H, d, J =17.0 Hz, NCH_2C=O), 2.68 (1H, d, J = 9.4 Hz, NCH_2C(Me)C$O_2{}^t$Bu), 2.40 (3H, s, NCH_3), 1.43 (9H, s, C(CH_3)$_3$), 1.33 (3H, s, CH_3); ^{13}C NMR (75.5, $CDCl_3$) δ 211.3, 170.5, 82.4, 65.2, 63.2, 58.8, 43.0, 28.2, 18.6; HRMS (ESI) calcd for $C_{11}H_{19}NNaO_3$ $[M+Na]^+$: m/z 236.1263, found 236.1259.

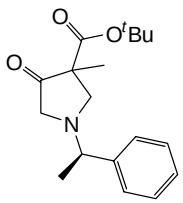
5.5 Asymmetric Molybdenum-Catalysed Reductive Dieckmann Condensation

5.5.1: Ligation of molybdenum



A solution of molybdenum hexacarbonyl (6.6 mg, 0.025 mmol), *N*-methylmorphonline *N*-oxide monohydrate (5.9 mg, 0.044 mmol) and (+)-dolefin **266** (15.5 mg, 0.05 mmol) was stirred in tetrahydrofuran (1 mL) for 45 minutes at 80 °C. After cooling to ambient temperature *tert*-butyl 2-((benzyl(2-ethoxy-2-oxoethyl)amino)methyl)acrylate **222** (167 mg, 0.5 mmol) and phenylsilane (92 μL, 0.75 mmol). The reaction mixture was stirred at 80 °C for 16 hours. After cooling to room temperature the reaction mixture was dissolved in diethyl ether (25 mL) and washed with water (2 x 25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (12:1 petrol:diethyl ether) to give the desired product **258** as a colourless oil (127 mg, 88%); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): t_R = 15.3 min, t_R = 16.5 min, 0% ee. Spectroscopic data identical to that previously reported (*cf*. 5.9.1).

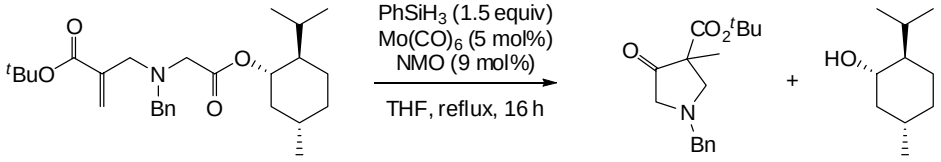
5.5.2: *tert*-butyl 3-methyl-4-oxo-1-((*R*)-1-phenylethyl)pyrrolidine-3-carboxylate 276



To a solution of molybdenum hexacarbonyl (6.6 mg, 0.025 mmol, 5 mol%) and *N*-methylmorpholine *N*-oxide monohydrate (5.9 mg, 0.044 mmol, 9 mol%) in tetrahydrofuran (3 mL) was added (*R*)-*tert*-butyl 2-(((2-ethoxy-2-oxoethyl)(1-phenylethyl)amino)

methyl)acrylate **275** (174 mg, 0.5 mmol) followed by phenylsilane (92 μL, 0.75 mmol). The reaction mixture was stirred at 80 °C for 16 hours. After cooling to room temperature the reaction mixture was dissolved in diethyl ether (25 mL) and washed with water (2 x 25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (12:1 petrol:ethyl acetate) to give the desired product, a colourless oil, as an inseparable 1:1 mixture of diastereomers (140.1 mg, 92%); R_f (12:1 petrol:ethyl acetate) 0.22; IR (neat, cm^{-1}) ν 2976, 2934 (C-H), 1764, 1728 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.22 (5H, m, Ar), 3.36 (0.5H, q, J = 6.8 Hz, NC*H*), 3.33 (0.5H, q, J = 6.8 Hz, NC*H*), 3.30 (0.5H, d, J = 17.0 Hz, NCH_2CO), 3.27 (0.5H, d, J = 9.4 Hz, NCH_2C(Me)$CO_2{}^t$Bu), 3.23 (0.5H, d, J = 9.4 Hz, NCH_2C(Me)$CO_2{}^t$Bu), 3.07 (1H, s, NCH_2CO), 2.87 (0.5H, d, J = 17.0 Hz, NCH_2CO), 2.58 (0.5H, d, J = 9.4 Hz, NCH_2C(Me)$CO_2{}^t$Bu), 2.54 (0.5H, d, J = 9.4 Hz, NCH_2C(Me)$CO_2{}^t$Bu), 1.44 (4.5H, s, C(CH_3)$_3$), 1.43 (4.5H, s, C(CH_3)$_3$), 1.36 (1.5H, d, J = 6.8 Hz, NCHCH_3), 1.35 (1.5H, d, J = 6.8 Hz, NCHCH_3), 1.32 (1.5H, s, C($CO_2{}^t$Bu)CH_3), 1.29 (1.5H, s, C($CO_2{}^t$Bu)CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.1 (2C), 170.8 and 170.7, 144.3 (2C), 128.9 (2C), 127.7 (2C), 127.4 (2C), 82.3 and 82.2, 65.3 and 65.2, 61.7 and 61.6, 60.5 and 60.4, 58.3 (2C), 28.5 and 28.3, 22.8 (2C), 18.1 and 17.9; HRMS (ESI) calcd for $C_{18}H_{26}NO_3$ $[M+H]^+$: m/z 304.1913, found 304.1912.

5.5.3: Reductive Dieckmann Condensation of 292



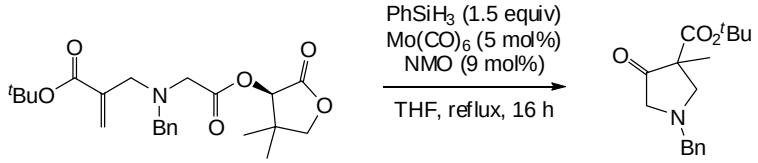
To a solution of molybdenum hexacarbonyl (6.6 mg, 0.025 mmol, 5 mol%) and *N*-methylmorpholine *N*-oxide monohydrate (5.9 mg, 0.044 mmol, 9 mol%) in tetrahydrofuran (3 mL) was added *tert*-butyl 2-((benzyl(2-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl) acrylate **292** (222 mg, 0.5 mmol) followed by phenylsilane (92 μL, 0.75 mmol). The reaction mixture was stirred at 80 °C for 16 hours. After cooling to room temperature the reaction mixture was dissolved in diethyl ether (25 mL) and washed with water (2 x 25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was

purified by flash column chromatography (12:1 petrol:diethyl ether) to give the desired product **258** as a colourless oil (115 mg, 79%), followed by (+)-menthol **293** as colourless crystals (93.3 mg, 60%).

Data for **258**: HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 18.4 min, t_R (major) = 20.4 min, 44% ee. All other spectroscopic data identical to that previously reported (*cf*. 5.9.1).

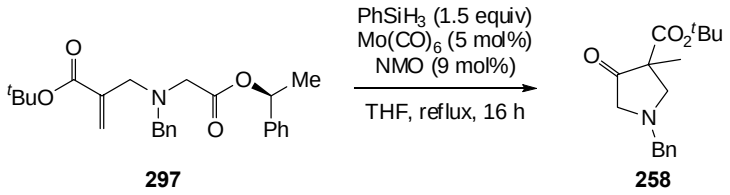
Data for **293**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38-3.30 (1H, m), 2.15 (1H, sept.d, J^1 = 6.8 Hz, J^2 = 2.6 Hz), 1.95-1.88 (2H, m), 1.64-1.53 (2H, m), 1.45-1.29 (1H, m), 1.11-1.02 (1H, m), 0.99-0.81 (3H, m), 0.88 (3H, d, J = 6.8 Hz), 0.87 (3H, d, J = 6.8 Hz), 0.76 (3H, d, J = 7.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 71.3, 50.0, 45.0, 34.5, 31.6, 25.6, 23.0, 22.1, 20.9, 16.0. **293** is commercially available.

5.5.4: Reductive Dieckmann Condensation of 296



To a solution of molybdenum hexacarbonyl (5.4 mg, 0.02 mmol, 5 mol%) and *N*-methylmorpholine *N*-oxide monohydrate (4.8 mg, 0.033 mmol, 9 mol%) in tetrahydrofuran (3 mL) was added *(R)-tert*-butyl 2-((benzyl(2-(4,4-dimethyl-2-oxotetrahydrofuran-3-yloxy)-2-oxoethyl)amino)methyl)acrylate **296** (170 mg, 0.41 mmol) followed by phenylsilane (75 μL, 0.62 mmol). The reaction mixture was stirred at 80 ^{o}C for 16 hours. After cooling to room temperature the reaction mixture was dissolved in diethyl ether (25 mL) and washed with water (2 x 25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (12:1 petrol:diethyl ether) to give the desired product **258** as a colourless oil (76.4 mg, 65%); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 15.8 min, t_R (major) = 17.3 min, 9% ee. Spectroscopic data identical to that previously reported (*cf*. 5.9.1).

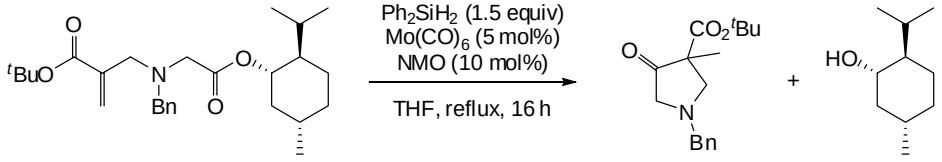
5.5.5: Reductive Dieckmann Condensation of 297



297 **258**

To a solution of molybdenum hexacarbonyl (6.6 mg, 0.025 mmol, 5 mol%) and *N*-methylmorpholine *N*-oxide monohydrate (5.9 mg, 0.044 mmol, 9 mol%) in tetrahydrofuran (3 mL) was added *tert*-butyl (*S*)-*tert*-butyl 2-((benzyl(2-oxo-2-(1-phenylethoxy)ethyl)amino)methyl)acrylate **292** (205 mg, 0.5 mmol) followed by phenylsilane (92 μL, 0.75 mmol). The reaction mixture was stirred at 80 ^{o}C for 16 hours. After cooling to room temperature the reaction mixture was dissolved in diethyl ether (25 mL) and washed with water (2 x 25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (12:1 petrol:diethyl ether) to give the desired product **258** as a colourless oil (94.9 mg, 66%); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 15.3 min, t_R (major) = 16.7 min, 2% ee. Spectroscopic data identical to that previously reported (*cf*. 5.9.1).

5.5.6: Reductive Dieckmann Condensation of 292 Mediated by Diphenylsilane



292

258 : 85% yield
20% ee

293 : 62%

To a solution of molybdenum hexacarbonyl (6.6 mg, 0.025 mmol, 5 mol%) and *N*-methylmorpholine *N*-oxide monohydrate (5.9 mg, 0.044 mmol, 9 mol%) in tetrahydrofuran (3 mL) was added *tert*-butyl 2-((benzyl(2-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl) acrylate **292** (222 mg, 0.5 mmol) followed by diphenylsilane (139 μL, 0.75 mmol). The reaction mixture was stirred at 80 ^{o}C for 16 hours. After cooling to room temperature the reaction mixture was dissolved in diethyl ether (25 mL) and washed with water (2 x 25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (12:1 petrol:diethyl ether) to give the desired

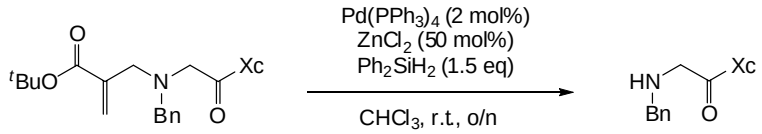
product **258** as a colourless oil (127 mg, 85%), followed by (+)-menthol **293** as colourless crystals (96.8 mg, 62%).

Data for **258**: HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 16.1 min, t_R (major) = 17.6 min, 20% ee. All other spectroscopic data identical to that previously reported (*cf*. 5.9.1).

Data for **293**: All data identical to that previously reported (*cf*. 5.5.3).

5.6 Palladium-Catalysed Deallylation

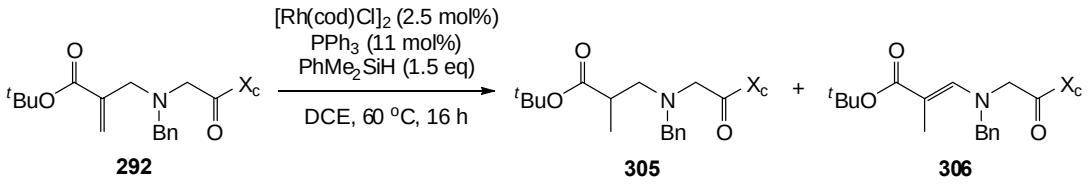
5.6.1: (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-(benzylamino)acetate 291



To a solution of *tert*-butyl 2-((benzyl(2-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl) acrylate **292** (88.7 mg, 0.2 mmol) in chloroform (2 mL) was added diphenylsilane (76 μL, 0.3 mmol), zinc chloride (13.6 mg, 0.1 mmol) and $Pd(PPh_3)_4$ (4.6 mg, 0.004 mmol). The reaction mixture was stirred at ambient temperature for 20 hours. The reaction mixture was filtered through a short silica column and concentrated in vacuo to give the desired product as a colourless oil (84.9 mg, 96% yield). Spectroscopic data identical to that previously reported (*cf.* 5.3.8).

5.7 Rhodium-Catalysed Reduction

5.7.1: *tert*-butyl 3-(benzyl(2-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)-2-methylpropanoate 305 and *tert*-butyl 3-(benzyl(2-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)-2-methylacrylate 306



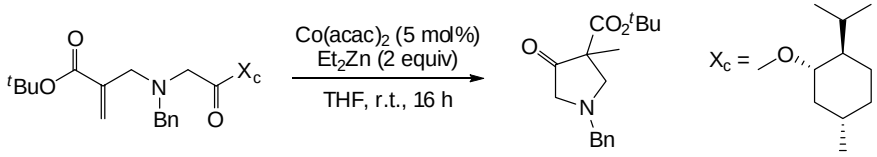
A solution of $[Rh(cod)Cl]_2$ (2.5 mg, 0.01 mmol, 5 mol% Rh) and triphenylphosphine (6.8 mg, 0.026 mmol 13 mol%) in dichloromethane (2 mL) was stirred under an atmosphere of argon for 30 minutes. *tert*-Butyl 2-((benzyl(2-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl) acrylate **292** (88.7 mg, 0.2 mmol) was added to the solution, followed by dimethylphenylsilane (46 μL, 0.3 mmol) and the resultant mixture was stirred at 60 °C for 16 hours. After cooling to room temperature, water (0.5 mL) was added and was left to stir for 15 minutes before the reaction mixture was dissolved in DCM, dried over $MgSO_4$, concentrate *in vacuo*. The residue was purified by flash column chromatography (17:1 petrol:diethyl ether) to give **305** as a colourless oil (8.1 mg, 9%) followed by **306** as a colourless oil (34.5 mg, 40%).

Data for **305**: R_f (17:1 petrol:diethyl ether) 0.28; IR (neat, cm^{-1}) *v* 2955, 2979 (C-H), 1730 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.21 (5H, m, Ar), 4.72 (1H, td, J^1 = 10.9 Hz, J^2 = 4.5 Hz, OC*H*), 3.83 (2H, s, NCH_2Ph), 3.27 (2H, s, NCH_2COX_c), 3.00 (1H, dd, J^1 = 12.8 Hz, J^2 = 9.0 Hz, $NCH_2CH(Me)CO_2{}^tBu$), 2.78 (1H, dd, J^1 = 12.8 Hz, J^2 = 6.4 Hz, $NCH_2CH(Me)CO_2{}^tBu$), 2.64-2.52 (1H, m, $CH(Me)CO_2{}^tBu$), 2.03-1.96 (1H, m, *mentholate*), 1.87-1.75 (1H, m, *mentholate*), 1.71-1.63 (2H, m, *mentholate*), 1.50-1.21 (3H, m, *mentholate*), 1.45 (9H, s, $C(CH_3)_3$, 1.03 (3H, d, *J* = 7.2 Hz, $^tBuO_2CCHCH_3$), 1.04-0.83 (2H, m, *mentholate*), 0.91 (3H, d, *J* = 6.5 Hz, $CH(CH_3)_2$), 0.88 (3H, d, *J* = 6.5 Hz, $CH(CH_3)_2$), 0.77 (3H, d, *J* = 6.8 Hz, $CHCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.9, 166.0, 137.0, 129.4, 128.6, 127.5, 80.6, 74.6, 60.1, 59.8, 56.2, 47.4, 41.5, 40.5, 34.6, 31.8, 28.5, 26.6, 23.7, 22.4, 21.2, 16.6, 15.7; HRMS (ESI) calcd for $C_{27}H_{44}NO_4$ $[M+H]^+$: *m*/*z* 446.3270, found 446.3271.

Data for **306:** R_f (17:1 petrol:diethyl ether) 0.09; $[\alpha]_D^{24}$ +55.5 (c 1.4, $CHCl_3$); IR (neat, cm^{-1}) *v* 2956, 2929, 2870 (C-H), 1740, 1683 (C=O), 1628, 1605 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (1H, s, C=C*H*N) 7.39-7.23 (5H, m, Ar), 4.74 (1H, td, J^1 = 10.9 Hz, J^2 = 4.5 Hz, OC*H*), 4.48 (2H, s, NCH_2Ph), 3.87 (2H, s, NCH_2COX$_c$), 3.00 (1H, dd, J^1 = 12.8 Hz, J^2 = 9.0 Hz, NCH_2CH(Me)$CO_2{}^t$Bu), 2.78 (1H, dd, J^1 = 12.8 Hz, J^2 = 6.4 Hz, NCH_2CH(Me)$CO_2{}^t$Bu), 2.64-2.52 (1H, m, C*H*(Me)$CO_2{}^t$Bu), 2.01-1.94 (1H, m, *mentholate*), 1.85 (3H, s, CH_3C=C), 1.87-1.74 (1H, m, *mentholate*), 1.70-1.64 (2H, m, *mentholate*), 1.55-1.26 (2H, m, *mentholate*), 1.46 (9H, s, C(CH_3)$_3$, 1.11-0.83 (3H, m, *mentholate*), 0.91 (3H, d, *J* = 6.5 Hz, CH(CH_3)$_2$), 0.88 (3H, d, *J* = 6.5 Hz, CH(CH_3)$_2$), 0.75 (3H, d, *J* = 6.8 Hz, CHCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.5, 170.1, 148.0, 137.5, 129.2, 129.0, 128.1, 97.4, 79.1, 75.9, 58.9, 52.8, 47.4, 41.2, 34.5, 31.8, 28.8, 26.6, 23.7, 22.4, 21.1, 16.6, 11.7; HRMS (ESI) calcd for $C_{27}H_{44}NO_4$ $[M+H]^+$: *m*/*z* 444.3114, found 446.3124.

5.8 Cobalt-Catalysed Reductive Dieckmann Condensation

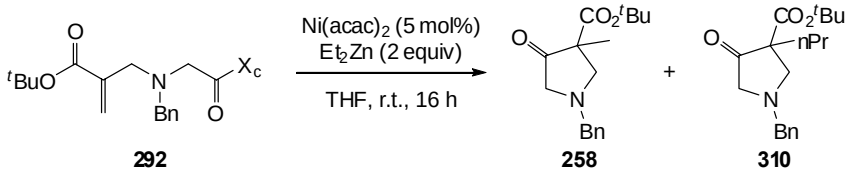
5.8.1: *tert*-butyl 1-benzyl-3-methyl-4-oxopyrrolidine-3-carboxylate 258



A solution of $Co(acac)_2$ (2.7 mg, 0.01 mmol, 5 mol%) and *tert*-butyl 2-((benzyl(2-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl)acrylate **292** (88.7 mg, 0.2 mmol) in tetrahydrofuran (3 mL) was stirred at room temperature for 15 minutes before cooling to 0 ^{o}C. Diethylzinc (1 M in hexanes) (400 μL, 0.4 mmol) was added to the solution, the reaction mixture was stirred at ambient temperature for 16 hours. 1 M $HCl_{(aq)}$ (1 mL) was added to the reaction mixture and the resulting solution was stirred for 15 minutes. The reaction mixture was dissolved in diethyl ether (25 mL) and washed with saturated sodium hydrogen carbonate (2 x 25 mL), water (25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flashed column chromatography (12:1 petrol:diethyl ether) to give **258** as a colourless oil (25.6 mg, 44%); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 15.4 min, t_R (major) = 16.6 min, 29% ee. All other spectroscopic data identical to that previously reported (*cf*. 5.9.1).

5.9 Nickel-Catalysed Reductive Dieckmann Condensation

5.9.1: *tert*-butyl 1-benzyl-4-oxo-3-propylpyrrolidine-3-carboxylate 310 and *tert*-butyl 1-benzyl-4-oxo-3-propylpyrrolidine-3-carboxylate 258



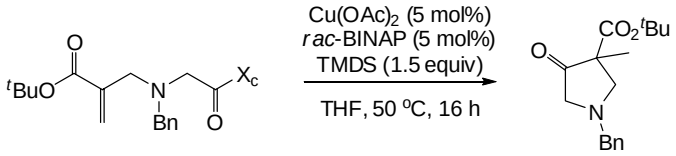
A solution of $Ni(acac)_2$ (2.7 mg, 0.01 mmol, 5 mmol%) and *tert*-butyl 2-((benzyl(2-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl)acrylate **292** (88.7 mg, 0.2 mmol) in tetrahydrofuran (3 mL) was stirred at room temperature for 15 minutes before cooling to 0 ^{o}C. Diethylzinc (1 M in hexanes) (400 μL, 0.4 mmol) was added to the solution, the reaction mixture was stirred at ambient temperature for 16 hours. 1 M $HCl_{(aq)}$ (1 mL) was added to the reaction mixture and the resulting solution was stirred for 15 minutes. The reaction mixture was dissolved in diethyl ether (25 mL) and washed with saturated sodium hydrogen carbonate (2 x 25 mL), water (25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flashed column chromatography (12:1 petrol:diethyl ether) to give *tert*-butyl 1-benzyl-4-oxo-3-propylpyrrolidine-3-carboxylate **310** as a colourless oil (18.3 mg, 29% yield) followed by **258** as a colourless oil (38.7 mg, 67%).

Data for **310**: R_f (12:1 petrol:diethyl ether) 0.24; IR (neat, cm^{-1}) ν 2963, 2933, 2874, 2797 (C-H), 1762, 1725 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.20 (5H, m, Ar-*H*), 3.70 (1H, d, J = 13.2 Hz, NCH_2Ph), 3.64 (1H, d, J = 13.2 Hz, NCH_2), 3.37 (1H, d, J = 9.4 Hz, NCH_2C(^{n}Pr)$CO_2{}^t$Bu), 3.19 (1H, d, J = 17.0 Hz, NCH_2CO), 2.88 (1H, d, J = 17.0 Hz, NCH_2CO), 2.64 (1H, d, J = 9.4 Hz, NCH_2C(^{n}Pr)$CO_2{}^t$Bu), 1.81 (1H, ddd, J = 13.9 Hz, 12.4 Hz, 4.5 Hz, C($CO_2{}^t$Bu)C$H_2$$CH_2CH_3$), 1.64 (1H, ddd, J = 13.9 Hz, 12.4 Hz, 4.5 Hz, C($CO_2{}^t$Bu)C$H_2$$CH_2CH_3$), 1.51-1.34 (1H, m, C($CO_2{}^t$Bu)$CH_2CH_2$$CH_3$), 1.42 (9H, s, C($CH_3$)$_3$), 1.27-1.12 (1H, m, C($CO_2{}^t$Bu)$CH_2CH_2$$CH_3$), 0.87 (3H, t, J = 7.2 Hz, C($CO_2{}^t$Bu)$CH_2CH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.1, 169.6, 138.0, 129.3, 128.8, 127.7, 82.3, 62.6, 61.6, 60.4, 60.3, 35.1, 28.3, 18.7, 14.9; HRMS (ESI) calcd for $C_{19}H_{28}NO_3$ $[M+H]^+$: m/z 318.2069, found 318.2074.

Data for **258**: HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 14.6 min, t_R (major) = 15.6 min, 18% ee. All other spectroscopic data identical to that previously reported (*cf*. 5.9.1).

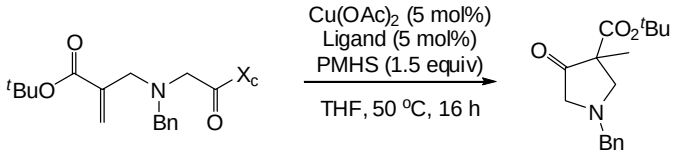
5.10 Copper-Catalysed Reductive Dieckmann Condensation

5.10.1: Reductive Dieckmann Condensation of 292 Mediated by Tetramethyldisiloxane



A solution of $Cu(OAc)_2$ (1.8 mg, 0.01 mmol, 5 mol%) and *rac*-BINAP (6.4 mg, 0.01 mmol, 5 mol%) in tetrahydrofuran (1 mL) was stirred at ambient temperature for 15 minutes before the addition of tetramethyldisiloxane (53 μL, 0.3 mmol). The resulting solution was stirred for a further 10 minutes, after which, a solution of *tert*-butyl 2-((benzyl(2-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl) acrylate **292** (88.7 mg, 0.2 mmol) in tetrahydrofuran (2 mL) was added *via* syringe. The reaction was stirred at 50 °C for 16 hours. The crude reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (12:1 petrol:diethyl ether) to give **258** as a colourless oil (11.5 mg, 20%); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): t_R (minor) = 17.2 min, t_R (major)= 18.6 min, 41% ee. All other spectroscopic data identical to that previously reported (*cf*. 5.9.1).

5.10.2: Reductive Dieckmann Condensation of 292 Using Achiral Bisphosphine Ligands



A solution of $Cu(OAc)_2$ (1.8 mg, 0.01 mmol, 5 mol%) and achiral bisphosphine ligand (0.01 mmol, 5 mol%) in tetrahydrofuran (1 mL) was stirred at ambient temperature for 15 minutes before the addition of polymethylhydrosiloxane (20 μL, 0.3 mmol). The resulting solution was stirred for a further 10 minutes, after which, a solution of *tert*-butyl 2-((benzyl(2-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl) acrylate **292** (88.7 mg, 0.2 mmol) in tetrahydrofuran (2 mL) was added *via* syringe. The reaction was stirred at 50 °C for 16 hours. The crude reaction mixture was concentrated *in*

vacuo and purified by flash column chromatography (12:1 petrol:diethyl ether) to give **258** as a colourless oil.

5.10.2.1: dppf

dppf (5.7 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (24.8 mg, 43% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 17.3 min, t_R (major) = 19.0 min, 36% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

5.10.2.2: *rac*-BINAP

rac-BINAP (6.2 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (34.3 mg, 59% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 14.8 min, t_R (major) = 16.0 min, 48% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

5.10.2.3: dppm

dppm (3.8 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (12.3 mg, 21% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 17.1 min, t_R (major) = 18.7 min, 44% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

5.10.2.4: dppe

dppe (4.0 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (39.4 mg, 68% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 15.0 min, t_R (major)

= 16.2 min, 50% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

5.10.2.5: dppp

dppp (4.1 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (52.1 mg, 73% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 15.0 min, t_R (major) = 16.2 min, 46% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

5.10.2.6: dppb

dppb (4.3 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (11.8 mg, 20% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 17.5 min, t_R (major) = 19.2 min, 43% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

5.10.2.7: dcpe

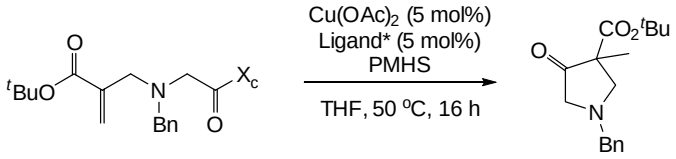
dcpe (4.2 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (45.3 mg, 78% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 15.1 min, t_R (major) = 16.2 min, 40% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

5.10.2.8: Xantphos

Xantphos **311** (5.8 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (36.1 mg, 62% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 15.2 min, t_R (major)

= 16.4 min, 30% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

5.10.3: Reductive Dieckmann Condensation of 292 Using Chiral Bisphosphine Ligands



A solution of $Cu(OAc)_2$ (1.8 mg, 0.01 mmol, 5 mol%) and chiral bisphosphine ligand (0.01 mmol, 5 mol%) in tetrahydrofuran (1 mL) was stirred at ambient temperature for 15 minutes before the addition of polymethylhydrosiloxane (20 μL, 0.3 mmol). The resulting solution was stirred for a further 10 minutes, after which, a solution of *tert*-butyl 2-((benzyl(2-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl) acrylate **292** (88.7 mg, 0.2 mmol) in tetrahydrofuran (2 mL) was added *via* syringe. The reaction was stirred at 50 °C for 16 hours. The crude reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (12:1 petrol:diethyl ether) to give **258** as a colourless oil.

5.10.3.1: (*R*)-BINAP

(*R*)-BINAP (*R*)-52 (6.2 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (15.5 mg, 27% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): t_R (minor) = 15.4 min, t_R (major) = 16.8 min, 79% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

5.10.3.2: (*S*)-BINAP

(*S*)-BINAP (*S*)-52 (6.2 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (36.1 mg, 62% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): t_R (minor) = 15.5 min, t_R (major)

= 16.8 min, 14% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

5.10.3.3: (*R*)-Tol-BINAP

(*R*)-Tol-BINAP 312 (6.8 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (26.1 mg, 45% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 15.1 min, t_R (major) = 16.3 min, 75% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

5.10.3.4: (*R*)-Xylyl-BINAP

(*R*)-Xylyl-BINAP 313 (7.4 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (46.0 mg, 79% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 14.8 min, t_R (major) = 15.9 min, 35% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

5.10.3.5: (*R*,*R*)-^{i}Pr-DuPhos

(*R*,*R*)-^{i}Pr-DuPhos 315 (4.2 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (38.2 mg, 66% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 17.7 min, t_R (major) = 19.4 min, 46% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

5.10.3.6: (*R*,*R*)-Me-DuPhos

(*R*,*R*)-Me-Duphos 314 (3.1 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (39.5 mg, 68% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 15.2 min, t_R

(major) = 16.3 min, 86% ee. All other spectroscopic data identical to that previously reported (*cf*. 5.9.1).

5.10.3.7: (*R*)-(*S*)-Josiphos

(*R*)-(*S*)-Josiphos 316 (6.4 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (49.7 mg, 86% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 16.0 min, t_R (major) = 17.3 min, 45% ee. All other spectroscopic data identical to that previously reported (*cf*. 5.9.1).

5.10.3.8: (*S*)-(*R*)-Josiphos

(*S*)-(*R*)-Josiphos 317 (6.4 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (57.6 mg, 99% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 137 min, t_R (major) = 14.8 min, 48% ee. All other spectroscopic data identical to that previously reported (*cf*. 5.9.1).

5.10.3.9: (*R*)-PhanePhos

(*R*)-PhanePhos 318 (5.8 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (30.4 mg, 53% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 15.3 min, t_R (major) = 16.7 min, 15% ee. All other spectroscopic data identical to that previously reported (*cf*. 5.9.1).

5.10.3.10: (*R*)-SYNPHOS

(*R*)-SYNPHOS 317 (6.4 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (30.3 mg, 52% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 14.8 min, t_R (major)

= 16.0 min, 65% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

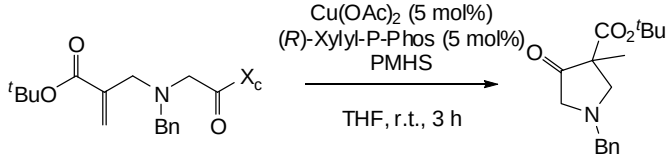
5.10.3.11: (*R*)-P-Phos

(*R*)-P-Phos 319 (6.4 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (44.9 mg, 78% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 17.7 min, t_R (major) = 19.5 min, 63% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

5.10.3.12: (*R*)-Xylyl-P-Phos

(*R*)-Xylyl-P-Phos 320 (7.6 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (33.7 mg, 58% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 15.2 min, t_R (major) = 16.4 min, 91% ee. All other spectroscopic data identical to that previously reported (*cf.* 5.9.1).

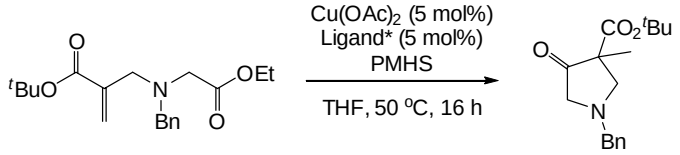
5.10.4: Room Temperature Reductive Dieckmann Condensation of 292



A solution of $Cu(OAc)_2$ (1.8 mg, 0.01 mmol, 5 mol%) and (*R*)-Xylyl-P-Phos **320** (6.4 mg, 0.01 mmol, 5 mol%) in tetrahydrofuran (1 mL) was stirred at ambient temperature for 15 minutes before the addition of polymethylhydrosiloxane (20 μL, 0.3 mmol). The resulting solution was stirred for a further 10 minutes, after which, a solution of *tert*-butyl 2-((benzyl(2-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl) acrylate **292** (88.7 mg, 0.2 mmol) in tetrahydrofuran (2 mL) was added *via* syringe. The reaction was stirred at ambient temperature for 3 hours. The crude reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (12:1 petrol:diethyl ether) to give **258** as a colourless oil (27.1 mg, 47%); HPLC Diacel Chiralpak OJ,

hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): t_R (minor) = 15.2 min, t_R (major) = 16.4 min, 93% ee; $[\alpha]_D^{24}$ +19.6 (c = 1.1, $CHCl_3$). All other spectroscopic data identical to that previously reported (*cf*. 5.9.1).

5.10.5: Reductive Dieckmann Condensation of 222 Using Chiral Bisphosphine Ligands



A solution of $Cu(OAc)_2$ (1.8 mg, 0.01 mmol, 5 mol%) and chiral bisphosphine ligand (0.01 mmol, 5 mol%) in tetrahydrofuran (1 mL) was stirred at ambient temperature for 15 minutes before the addition of polymethylhydrosiloxane (20 μL, 0.3 mmol). The resulting solution was stirred for a further 10 minutes, after which, a solution of *tert*-butyl 2-((benzyl(2-ethoxy-2-oxoethyl)amino)methyl) acrylate **222** (66.7 mg, 0.2 mmol) in tetrahydrofuran (2 mL) was added *via* syringe. The reaction was stirred at 50 °C for 16 hours. The crude reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (12:1 petrol:diethyl ether) to give **258** as a colourless oil.

5.10.5.1: (*R*,*R*)-^{i}Pr-DuPhos

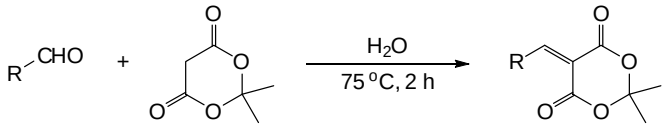
(*R*,*R*)-^{i}Pr-DuPhos 315 (4.2 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (15.3 mg, 26% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): t_R (minor) = 15.0 min, t_R (major) = 16.3 min, 20% ee. All other spectroscopic data identical to that previously reported (*cf*. 5.9.1).

5.10.5.2: (*R*,*R*)-Me-DuPhos

(*R*,*R*)-Me-Duphos 314 (3.1 mg, 0.01 mmol) was reacted under the standard procedure to give the desired product as a colourless oil (45.6 mg, 79% yield); HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 °C): t_R (minor) = 15.3 min, t_R

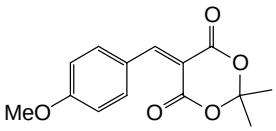
(major) = 16.6 min, 15% ee. All other spectroscopic data identical to that previously reported (*cf*. 5.9.1).

5.11 General Procedure for the Synthesis of Alkylidene Meldrum's Acid Derivatives



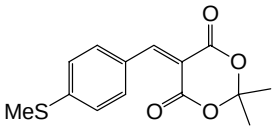
To a solution of Meldrum's acid (1.1 equiv) in water was added aldehyde (1.0 equiv). The resulting solution was stirred at 75 °C for 2 hours. After cooling the reaction mixture was filtered *via* Buckner filtration and washed with water (100 mL) and petrol (100 mL). The resulting solid was recrystallised from hot ethanol to give the desired compound.

5.11.1: 5-(4-methoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328a



Meldrum's acid (4.66 g, 32.3 mmol), *p*-anisaldehyde (3.58 mL, 29.4 mmol) and water (50 mL) were reacted the standard procedure to give the desired compound as a yellow crystalline solid (5.58g, 72%); mp (EtOH) 125-126 °C (lit = 127-128 °C)[3]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (1H, s, C=C*H*), 8.19 (2H, d, *J* = 9.0 Hz, Ar*H*), 6.95 (2H, d, *J* = 9.0 Hz, Ar*H*), 3.88 (3H, s, OCH_3), 1.76 (6H, s, C(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.0, 164.4, 160.8, 158.3, 138.0, 125.1, 115.0, 111.3, 104.5, 56.1, 27.9; HRMS (ESI) calcd for $C_{14}H_{14}NaO_5$ $[M+Na]^+$: *m/z* 285.0739, found 285.0725. Data identical to literature values.[4]

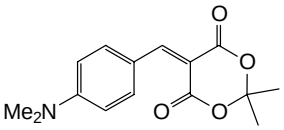
5.11.2: 5-(4-(Methylthio)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione 328b



Meldrum's acid (1.59 g, 11.0 mmol) and 4-(methylthio)benzaldehyde (1.52 g, 10.0 mmol) and water (20 mL) were reacted under the standard protocol to desired compound as a yellow crystalline solid (2.10 g, 75%); mp (EtOH) 126-128 °C; IR (KBr, cm^{-1}) *v* 3099, 2986, 2939 (C-H); 1750, 1711 (C=O); 1577 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (1H, s, C=C*H*); 8.11 (2H, d, *J* 6.8 Hz, Ar*H*); 7.32 (2H, d, *J* 6. 8 Hz, Ar*H*); 2.58 (3H, s, SCH_3), 1.83 (6H, s, C(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.6, 160.1, 157.4, 148.4, 134.6, 127.7, 124.7, 112.4, 104.2, 27.5, 14.4; HRMS (ESI) calcd for $C_{14}H_{18}NO_4S$

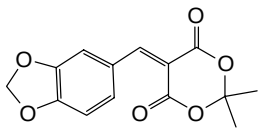
$[M+NH_4]^+$: *m*/*z* 296.0951, found 296.0951; Anal. calcd for $C_{14}H_{14}O_4S$: C 60.4, H 5.07, found: C 60.7, H 5.16.

5.11.3: 5-(4-dimethylaminobenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328c



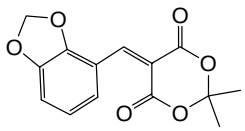
Meldrum's acid (793 mg, 5.5 mmol), 4-dimethylaminobenzaldehyde (746 mg, 5.0 mmol) in water (10 mL) was reacted under standard protocol to give the desired compound as a orange crystalline solid (1.26 g, 92%); mp (EtOH) 174-175 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (1H, s, C=C*H*), 8.25 (2H, d, *J* = 9.4 Hz, Ar*H*), 6.70 (2H, d, *J* = 9.4 Hz, Ar*H*), 3.15 (6H, s, N(CH_3)$_2$), 1.76 (6H, s, C(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.6, 161.9, 158.4, 155.0, 139.4, 120.5, 111.6, 105.4, 103.8, 40.5, 27.7; HRMS (ESI) calcd for $C_{15}H_{18}NO_4$ $[M+H]^+$: *m*/*z* 276.1236, found 276.1230. Data identical to literature values.[5]

5.11.4: 5-(benzo-[1,3]dioxol-5-ylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328d



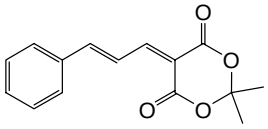
Meldrum's acid (1.25 g, 10.4 mmol), piperonal (1.50 g, 10.0 mmol) in water (20 mL) was reacted under standard protocol to give the desired compound as a yellow crystalline solid (2.54 g, 82 %); mp (EtOH) 178-180 ^oC (lit = 179-180 ^oC)[6]; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (1H, s, C=C*H*), 8.06 (1H, d, *J* = 1.9 Hz, Ar*H*), 7.54 (1H, dd, J^1 = 8.3 Hz, J^2 = 1.9 Hz, Ar*H*), 6.90 (1H, d, *J* = 8.3 Hz, Ar*H*), 6.09 (2H, s, OCH_2O), 1.78 (6H, s, C(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.3, 160.7, 158.3, 153.6, 148.7, 134.6, 126.8, 112.8, 111.7, 108.9, 104.7, 102.8, 27.9; HRMS (EI) calcd for $C_{14}H_{12}NaO_6$ $[M+Na]^+$: *m*/*z* 299.0532, found 299.0534. Data identical to literature values.[6]

5.11.5: 5-(benzo-[1,3]dioxol-4-ylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328e



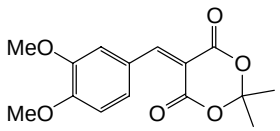
Meldrum's acid (1.25 g, 10.4 mmol), 2,3-(methylenedioxy)benzaldehyde (1.50 g, 10.0 mmol) in water (20 mL) was reacted under the standard protocol to give the desired compound as a yellow crystalline solid (2.03 g, 73%); mp (EtOH) 172-174 ^{o}C; IR (KBr, cm^{-1}) *v* 1740, 1710 (C=O), 1561 (C=C), 1382, 1248 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (1H, s, C=C*H*), 7.50 (1H, dd, J^1 = 7.5 Hz, J^2 = 1.5 Hz, Ar*H*), 6.95 (1H, dd, J^1 = 7.5 Hz, J^2 = 1.5 Hz, Ar*H*), 6.88 (1H, t, *J* = 7.5 Hz, Ar*H*), 6.06 (2H, s, OCH_2O), 1.80 (6H, s, C(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.2, 160.0, 149.8, 149.6, 148.2, 124.1, 122.1, 166.4, 115.4, 113.1, 105.1, 102.1, 28.0; HRMS (ESI) calcd for $C_{14}H_{12}NaO_6$ $[M+Na]^+$: *m*/*z* 299.0532, found 299.0530; Anal. calcd for $C_{14}H_{12}O_6$: C 60.9, H 4.38, found: C 70.0, H 4.42.

5.11.6: 2,2-dimethyl-5-(3-phenyl-allylidene)-[1,3]dioxane-4,6-dione 328f



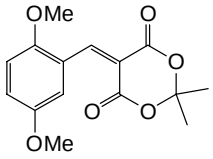
Meldrum's acid (793 mg, 5.5 mmol), cinnamaldehyde (629 μL, 5.0 mmol) and water (10 mL) was reacted under the standard protocol to give the desired product as a yellow crystalline solid (1.12 g, 87%); mp (EtOH) 98-99 ^{o}C (lit 101 ^{o}C)[7]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (1H, dd, J^1 = 15.1 Hz, J^2 = 12.1 Hz, PhCHC*H*), 8.19 (1H, d, *J* = 12.1 Hz, C=C*H*), 7.68-7.64 (2H, m, Ar*H*), 7.46-7.39 (4H, m, Ar*H* and PhC*H*), 1.76 (6H, s, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.4, 161.2, 158.4, 154.9, 135.3, 132.2, 129.7, 129.6, 124.9, 111.8, 105.2, 28.1; HRMS (ESI) calcd for $C_{15}H_{14}NaO_4$ $[M+Na]^+$: *m*/*z* 281.0790, found 281.0792. Data identical to literature values.[7]

5.11.7: 5-(3,4-dimethoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328g



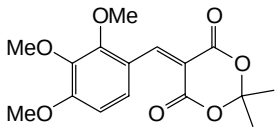
Meldrum's acid (1.59 g, 11.0 mmol), 3,4-dimethoxybenzaldehyde (1.66 g, 10 mmol) and water (20 mL) was reacted under the standard protocol to give the desired product as a yellow/orange crystalline solid (2.38 g, 81 %); mp (EtOH) 160-161 ^{o}C (lit = 156-158 ^{o}C)[4]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (1H, s, C=C*H*), 8.28 (1H, d, *J*= 2.3 Hz, Ar*H*), 7.62 (1H, dd, J^1 = 8.3 Hz, J^2 = 2.3 Hz, Ar*H*), 6.92 (1H, d, *J* = 8.3 Hz, Ar*H*), 3.97 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 1.77 (6H, s, C(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.5, 161.0, 158.6, 155.1, 149.1, 133.1, 125.5, 116.1, 111.1, 111.0, 104.6, 56.6, 56.4, 27.9; HRMS (EI) calcd for $C_{15}H_{17}O_6$ $[M+H]^+$: *m*/*z* 293.1020, found 293.1017. Data identical to literature values.[4]

5.11.8: 5-(2,5-dimethoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328h



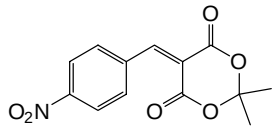
Meldrum's acid (1.59 g, 11.0 mmol), 2,5-dimethoxybenzaldehyde (1.66 g, 10 mmol) and water (20 mL) was reacted under standard protocol to give the desired compound as an orange crystalline solid (2.15 g, 73 %); mp (EtOH) 124-125 ^{o}C (lit = 120-121 ^{o}C)[8] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (1H, s, C=C*H*), 7.67 (1H, d, *J* = 3.0 Hz, Ar*H*), 7.08 (1H, dd, J^1 = 9.0 Hz, J^2 = 3.0 Hz, Ar*H*), 6.90 (1H, d, *J* = 9.0 Hz, Ar*H*), 3.85 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 1.80 (6H, s, C(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.7, 160.5, 154.8, 153.3, 152.8, 122.5, 121.9, 116.5, 115.4, 112.4, 104.8, 56.5, 56.3, 27.9; HRMS (EI) calcd for $C_{15}H_{16}NaO_6$ $[M+Na]^+$: *m*/*z* 315.0845, found 315.0856. Data identical to literature values.[8]

5.11.9: 5-(2,3,4-trimethoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328i



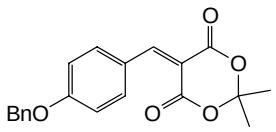
Meldrum's acid (793 mg, 5.5 mmol), 2,3,4-trimethoxybenzaldehyde (9.81 g, 5.5 mmol) and water (10 mL) was reacted under standard protocol to give the desired compound as a yellow crystalline solid (1.11 g, 69 %); mp (EtOH) 127-128 ^{o}C (lit = 123-124)[9]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (1H, s, C=C*H*), 8.16 (1H, d, *J* = 9.0 Hz, Ar*H*), 6.72 (1H, d, *J* = 9.0 Hz, Ar*H*), 3.99 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 1.78 (6H, s, C(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.1, 161.0, 159.6, 156.4, 153.0, 141.8, 129.6, 119.4, 112.6, 107.3, 104.6, 62.5, 61.4, 56.7, 27.9; HRMS (EI) calcd for $C_{16}H_{18}NaO_7$ $[M+Na]^+$: *m*/*z* 345.0950, found 345.0931. Data identical to literature values.[9]

5.11.10: 5-(4-nitrobenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328j



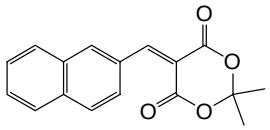
Meldrum's acid (4.66 g, 32.3 mmol), 4-nitrobenzaldehyde (4.44 g, 29.4 mmol) and water (50 mL) was reacted under the standard protocol to give the desired product as a pale orange solid (6.78 g, 83 %); mp (EtOH) 140-142 ^{o}C (lit 142-143 ^{o}C)[3]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (1H, s, C=C*H*), 8.30 (2H, d, *J* = 8.7 Hz, Ar*H*), 8.06 (2H, d, *J* = 8.7 Hz, Ar*H*), 1.84 (6H, s, C(CH_3)$_2$); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 162.0, 159.3, 154.2, 149.0, 138.9, 132.8, 123.5, 119.5, 105.5, 27.6; HRMS (ESI) calcd for $C_{13}H_{11}NNaO_6$ $[M+Na]^+$: *m*/*z* 300.0484, found 300.0482. Data identical to literature values.[3]

5.11.11: 5-(4-benzyloxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione 328k



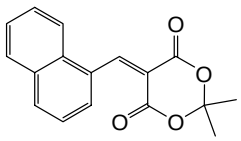
Meldrum's acid (6.34 g, 44.0 mmol), 4-benzyloxybenzaldehyde (8.49 g, 40.0 mmol) and water (100 mL) was reacted under the standard protocol to give the desired compound as a yellow crystalline solid (6.43 g, 48%); mp (EtOH) 118-120 ^{o}C; IR (KBr, cm^{-1}) *v* 1721, 1754 (C=O), 1216 (C-O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.37 (1H, s, C=C*H*), 8.22 (2H, d, *J* = 8.9 Hz, Ar*H*), 7.45–7.31 (5H, m, Ar*H*), 7.03 (2H, d, *J* = 8.9 Hz, Ar*H*), 5.17 (2H, s, OCH_2Ph), 1.78 (6H, s, C(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.5, 164.2, 160.9, 158.3, 138.0, 136.1, 129.2, 128.8, 12.9, 125.3, 115.6, 111.4, 104.6, 70.8, 27.9; HRMS (ESI) calcd for $C_{20}H_{18}NaO_5$ $[M+Na]^+$: *m*/*z* 361.1052, found 361.1048; Anal. calcd for $C_{20}H_{18}O_5$: C 71.0, H 5.36, found: C 70.8, H 5.44.

5.11.12: 2,2-dimethyl-5-(naphthalene-2-ylmethylene)-1,3,-dioxane-4,6-dione 328l



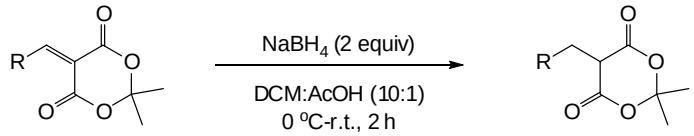
Meldrum's acid (793 mg, 5.5 mmol), 2-naphthaldehyde (781 mg, 5.0 mmol) and water (10 mL) was reacted under the standard protocol to give the desired product as a pale yellow crystalline solid (462 mg, 33 %); mp (EtOH) 148-150 ^{o}C; IR (KBr, cm^{-1}) *v* 1760, 1731, (C=O) 1607 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (1H, s, C=C*H*), 8.54 (1H, s, Ar*H*), 8.13 (1H, dd, J^1 = 8.7 Hz, J^2 = 1.9 Hz, Ar*H*), 7.94 (1H, d, *J* = 7.9 Hz, Ar*H*), 7.88 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.86 (1H, d, *J* = 7.9 Hz, Ar*H*), 7.63 (1H, ddd, J^1 = 7.9 Hz, J^2 = 6.8 Hz, J^3 = 1.5 Hz, Ar*H*), 7.55 (1H, ddd, J^1 = 7.9 Hz, J^2 = 6.8 Hz, J^3 = 1.5 Hz, Ar*H*), 1.84 (6H, s, C(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.9, 160.4, 158.6, 137.5, 136.0, 133.0, 130.2, 129.9, 129.8, 128.7, 128.5, 128.2, 127.4, 114.8, 105.0, 28.1; HRMS (ESI) calcd for $C_{17}H_{14}NaO_4$ $[M+Na]^+$: *m*/*z* 305.0790, found 305.0786; Anal. calcd for $C_{17}H_{12}O_4$: C 72.3, H 5.00, found: C 72.5, H 5.40.

5.11.13: 2,2-dimethyl-5-(naphthalen-1-ylmethylene)-1,3-dioxane-4,6-dione 328m



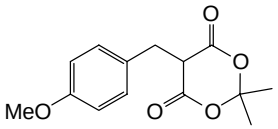
Meldrum's acid (4.66 g, 32.3 mmol), 1-naphthaldehyde (4.0 mL, 29.4 mmol) and water (50 mL) was reacted under the standard protocol to give the desired product as a pale yellow crystalline solid (6.4 g, 77 %); mp (EtOH) 140-141 ^{o}C; IR (KBr, cm^{-1}) *v* 1728 (C=O), 1608 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (1H, s, C=C*H*), 8.03-7.90 (4H, m, Ar*H*), 7.65-7.51 (3H, m, Ar*H*), 1.86 (6H, s, C(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.2, 159.9, 156.9, 133.7, 133.7, 132.1, 130.4, 129.6, 129.4, 128.2, 127.1, 125.3, 124.0, 117.4, 105.2, 28.2; HRMS (ESI) calcd for $C_{17}H_{18}NO_4$ $[M+NH_4]^+$: *m/z* 300.1230, found 300.1234.

5.12 General Procedure for the Synthesis of 5-Monoalkyl Meldrum's Acid Derivatives



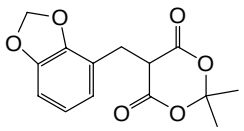
To a solution of 5-arylidene Meldrum's acid derivative and glacial acetic acid in dichloromethane at 0 ^{o}C was added sodium borohydride portion wise. The resulting solution was allowed to reach ambient temperature and stirred for 2 hour. The solution was dissolved in dichloromethane and washed with brine and water. The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo* to give the desired product.

5.12.1: 5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367a



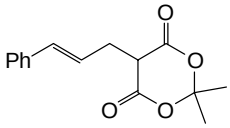
5-(4-methoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **328a** (1.00 g, 3.82 mmol), glacial acetic acid (4.0 mL), sodium borohydride (0.43 g, 11.4 mmol) and dichloromethane (25 mL) was reacted under the standard procedure to give the desired product as a white solid (994 mg, 98%); mp (EtOAc) 82-85 ^{o}C (lit = 85-86 ^{o}C)[10]; IR (KBr, cm^{-1}) *v* 3006, 2961, 2915 (C-H), 1787, 1746 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.82 (2H, d, *J* = 8.7 Hz, Ar*H*), 3.77 (3H, s, OCH_3), 3.72 (1H, t, *J* = 4.9 Hz, CH_2CH), 3.44 (2H, d, *J* = 4.9 Hz, ArCH_2), 1.72 (3H, s, CH_3), 1.48 (3H, s, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.9, 159.1, 131.4, 129.4, 114.3, 105.6, 55.6, 48.7, 31.9, 28.9, 27.8; HRMS (ESI) calcd for $C_{14}H_{15}O_5$ $[M-H]^-$: *m*/*z* 263.0919, found 263.0912. Anal. calcd for $C_{14}H_{16}O_5$: C 63.6, H 6.10, found: C 63.1, H 6.06. Data identical to literature data.[10]

5.12.2: 5-(benzo[*d*][1,3]dioxol-4-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 367e



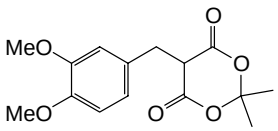
5-(benzo[*d*][1,3]dioxol-4-ylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **328e** (615 mg, 2.23 mmol), glacial acetic acid (2.0 mL), dichloromethane (10 mL) and sodium borohydride (168 mg, 4.45 mmol) was reacted under the standard protocol to give the desired compound as a white solid (569 mg, 92%); mp (EtOAc) 127-128 ^{o}C; IR (KBr, cm^{-1}) *v* 1755, 1725 (C=O), 1276 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (1H, d, *J* = 2.3 Hz, Ar*H*), 6.77 (1H, d, *J* = 6.8 Hz, Ar*H*), 6.72 (1H, dd, J^1 = 6.8 Hz, J^2 = 2.3 Hz, Ar*H*), 5.92 (2H, s, O-CH_2-O), 4.00 (1H, t, *J* = 5.7 Hz, CH_2CH), 3.40 (2H, d, *J* = 5.7 Hz, $ArCH_2$), 1.79 (3H, s, $C(CH_3)_2$), 1.71 (3H, s, $C(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.4, 147.6, 145.6, 123.6, 122.2, 119.5, 107.8, 105.5, 101.1, 46.4, 29.0, 27.0, 26.7; HRMS (ESI) calcd for $C_{14}H_{13}O_6$ $[M-H]^-$: *m*/*z* 277.0712, found 277.0694. Anal. calcd for $C_{14}H_{12}O_6$: C 60.9, H 4.40, found: C 59.9, H 4.30.

5.12.3: 5-cinnamyl-2,2-dimethyl-1,3-dioxane-4,6-dione 367f



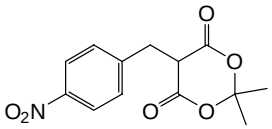
2,2-dimethyl-5-(3-phenyl-allylidene)-[1,3]dioxane-4,6-dione **328f** (233 mg, 0.90 mmol), glacial acetic acid (1.0 mL), dichloromethane (10 mL) and sodium borohydride (0.10 g, 2.71 mmol) was reacted under standard protocol to give the desired compound as a white solid (203 mg, 87%); mp (EtOAc) 85-86 ^{o}C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41-7.21 (5H, m, Ar), 6.63 (1H, d, *J* = 15.8 Hz, PhC*H*), 6.29 (1H, dt, J^1 = 15.8 Hz, J^2 = 7.3 Hz, PhCHC*H*), 3.70 (1H, t, *J* = 5.1 Hz, CH_2CH), 3.05 (2H, dd, J^1 = 7.3 Hz, J^2 = 5.1 Hz, $CHCH_2CH$), 1.81 (3H, s, $C(CH_3)_2$), 1.77 (3H, s, $C(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.4, 137.2, 135.1, 128.9, 128.0, 126.7, 124.3, 105.5, 47.0, 30.0, 28.8, 27.3; HRMS (ESI) calcd for $C_{15}H_{15}O_4$ $[M-H]^-$: *m*/*z* 259.0970, found 259.0970. Data identical to literature values.[11]

5.12.4: 5-(3,4-dimethoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367g



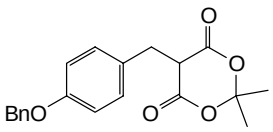
5-(3,4-dimethoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **328g** (585 mg, 2.0 mmol), glacial acetic acid (2.0 mL), dichloromethane (15 mL) and sodium borohydride (151 mg, 4.0 mmol) was reacted under the standard protocol to give the desired compound as a white solid (495 mg, 84%); mp (EtOAc) 138-140 ^{o}C (lit = 136-137 ^{o}C)[12]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (1H, d, *J* = 9.0 Hz, Ar*H*), 6.83 (1H, s, Ar*H*), 6.76 (1H, d, *J* = 9.0 Hz, Ar*H*), 3.84 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.74 (1H, t, *J* = 4.9 Hz, CH_2CH), 3.43 (2H, d, *J* = 4.9 Hz, CH_2CH), 1.71 (3H, s, CH_3), 1.47 (3H, s, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.9, 149.1, 148.5, 129.9, 122.4, 113.5, 111.5, 105.6, 56.3, 56.2, 48.7, 32.3, 28.9, 27.8; HRMS (ESI) calcd for $C_{15}H_{18}NaO_6$ $[M+Na]^+$: *m*/*z* 317.1001, found 317.0989. Data identical to literature values.[12]

5.12.5: 5-(4-nitrobenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367j



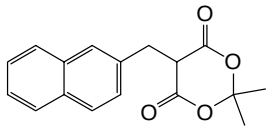
5-(4-nitrobenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **328j** (1.00 g, 3.61 mmol), glacial acetic acid (4.0 mL), dichloromethane (25 mL) and sodium borohydride (0.43 g, 11.4 mmol) was reacted under the standard protocol to give the desired compound as a pale yellow solid (881 mg, 87%); mp (EtOAc) 111-112 ^{o}C; IR (KBr, cm^{-1}) *v* 1758, 1730 (C=O), 1517, 1342 (N-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (2H, d, *J* = 8.7 Hz, Ar*H*), 7.53 (2H, d, *J* = 8.7 Hz, Ar*H*), 3.83 (1H, t, *J* = 5.3 Hz, CH_2CH), 3.44 (2H, d, *J* = 5.3 Hz, CH_2CH), 1.79 (3H, s, C(CH_3)$_2$), 1.67 (3H, s, C(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.0, 147.5, 145.1, 131.3, 124.1, 105.8, 48.1, 31.8, 28.8, 27.4; HRMS (ESI) calcd for $C_{13}H_{12}NO_6$ $[M-H]^-$: *m*/*z* 278.0665, found 278.0674; Anal. calcd for $C_{13}H_{13}NO_6$: C 55.9, H 4.69, N 5.02, found: C 55.7, H 4.75, N 4.98.

5.12.6: 5-(4-benzyloxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367k



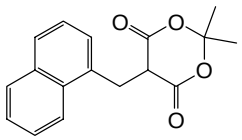
5-(4-benzyloxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **328k** (2.26 g, 6.68 mmol), glacial acetic acid (8.0 mL), dichloromethane (50 mL) and sodium borohydride (0.75 g, 20.0 mmol) was reacted under the standard protocol to give the desired compound as a white solid (2.10 g, 93%); mp (EtOAc) 92-94 ^{o}C; IR (KBr, cm^{-1}) *v* 3020, 2945, 2872 (C-H), 1785, 1748 (C=O); 1217 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.29 (5H, m, Ar*H*), 7.24 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.89 (2H, d, *J* = 8.7 Hz, Ar*H*), 5.03 (2H, s, O-CH_2-Ph), 3.73 (1H, t, *J* = 4.9 Hz, CH_2CH), 3.44 (2H, d, *J* = 4.9 Hz, CH_2CH), 1.72 (3H, s, $C(CH_3)_2$), 1.46 (3H, s, $C(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.9, 158.3, 137.3, 131.4, 129.8, 129.0, 128.4, 127.9, 115.3, 105.7, 70.3, 48.7, 31.9, 28.9, 27.8; HRMS (ESI) calcd for $C_{20}H_{20}NaO_5$ $[M+Na]^+$: *m*/*z* 363.1208, found 363.1203; Anal. calcd for $C_{20}H_{20}O_5$, C 70.6, H 5.92, found: C 71.3, H 5.88.

5.12.7: 2,2-dimethyl-5-(naphthalen-2-ylmethyl)-1,3-dioxane-4,6-dione 367l



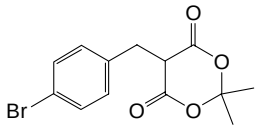
5-(naphthalene-2-methylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **328l** (201 mg, 0.71 mmol), glacial acetic acid (1.0 mL), dichloromethane (10 mL) and sodium borohydride (80.7 mg, 2.13 mmol) was reacted under the standard protocol to give the desired compound as a white solid (190 mg, 94%); mp (EtOAc) 128-129 ^{o}C; IR (KBr, cm^{-1}) *v* 3050, 2984, 2870 (C-H), 1790, 1745 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82-7.77 (4H, m, Ar*H*), 7.50-7.41 (3H, m, Ar*H*), 3.84 (1H, t, *J* = 4.9 Hz, CH_2CH), 3.65 (2H, d, *J* = 4.9 Hz, CH_2CH), 1.73 (3H, s, $C(CH_3)_2$), 1.50 (3H, s, $C(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.7, 135.2, 133.8, 132.9, 129.0, 128.7, 128.3, 128.2, 128.0, 126.5, 126.3, 105.6, 48.7, 32.6, 28.8, 27.6; HRMS (ESI) calcd for $C_{17}H_{15}O_4$ $[M-H]^-$: *m*/*z* 283.0970, found 283.0964.

5.12.8: 2,2-dimethyl-5-(naphthalen-1-ylmethyl)-1,3-dioxane-4,6-dione 367m



5-(naphthalene-1-methylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **328m** (1.15 g, 4.09 mmol), glacial acetic acid (2.5 mL), dichloromethane (25 mL) and sodium borohydride (464 mg, 12.3 mmol) was reacted under the standard protocol to give the desired compound as a white solid (1.12 g, 97%); mp (EtOAc) 135-137 ^{o}C; IR (KBr, cm^{-1}) 3057, 3000, 2869 (C-H); 1781, 1750 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (1H, dd, J^1 = 8.3 Hz, J^2 = 1.1 Hz, Ar*H*), 7.89 (1H, dd, J^1 = 8.3 Hz, J^2 = 1.5 Hz, Ar*H*), 7.79 (1H, d, J = 8.3 Hz, Ar*H*), 7.65 (1H, dd, J^1 = 7.2 Hz, J^2 = 1.1 Hz, Ar*H*), 7.57 (1H, ddd, J^1 = 8.3 Hz, J^2 = 6.8 Hz, J^3 = 1.5 Hz, Ar*H*), 7.51 (1H, ddd, J^1 = 8.3 Hz, J^2 = 6.8 Hz, J^3 = 1.5 Hz, Ar*H*), 7.44 (1H, dd, J^1 = 8.3 Hz, J^2 = 7.2 Hz, Ar*H*), 3.93 (1H, t, J = 5.3 Hz, C*H*CH_2Ar), 3.80 (2H, d, J = 5.3 Hz, CHC*H*$_2$Ar), 1.70 (3H, s, C(C*H*$_3$)$_2$), 1.69 (3H, s, C(C*H*$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.7, 134.5, 134.4, 131.7, 129.6, 128.8, 128.3, 127.1, 126.2, 126.0, 123.2, 105.6, 48.2, 29.2, 29.0, 26.9; HRMS (ESI) calcd for $C_{17}H_{15}O_4$ [M-H]$^-$: *m*/*z* 283.0970, found 283.0972. Data identical to literature values.[13]

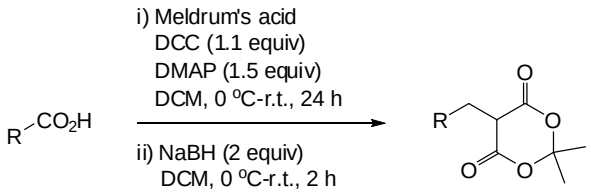
5.12: 5-(4-benzyloxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione 367n



4-bromobenzaldehyde (537 mg, 2.9 mmol) was added to a solution of Meldrum's acid (470 mg, 3.19 mmol) in water (10 mL). The solution was stirred at 75 ^{o}C for 2 h. After cooling the precipitate was filtered *via* Buckner filtration and washed with water (100 mL) and petrol (100 mL) and dried. The resulting solid was dissolved in dichloromethane (10 mL), acetic acid (2 mL) was added and the solution cooled to 0 ^{o}C. Sodium borohydride (219 mg, 5.8 mmol) was added portionwise, the solution allowed to warm to ambient temperature and was stirred for 2 h. The reaction mixture was dissolved in DCM (50 mL) and washed with water (3 x 50 mL) and brine (50 mL). The organic phase was separated, dried over $MgSO_4$ and concentrated *in vacuo* to give the desired product as a white solid (426 mg, 47 %); mp (EtOAc) 143-144 ^{o}C (lit = 142-144 ^{o}C)[14]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (2H, d, J = 8.3 Hz, Ar*H*), 7.21 (2H, d, J = 8.3 Hz, Ar*H*), 3.73 (1H, t, J = 4.9 Hz,

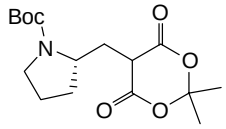
CH_2CH), 3.43 (2H, d, J = 4.9 Hz, CH_2CH), 1.75 (3H, s, $C(CH_3)_2$), 1.59 (3H, s, $C(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.4, 136.5, 132.1, 121.7, 105.6, 48.3, 31.8, 28.8, 27.6; HRMS (ESI) calcd for $C_{13}H_{14}BrO_4$ $[M+H]^+$: m/z 313.0075, found 313.0081. Data identical to literature values.[14]

5.13 The Reductive Coupling of *N*-Boc Protected Amino Acids and Meldrum's Acid



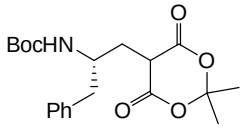
To a solution of *N*-Boc amino acid (20.0 mmol) and Meldrum's acid (3.02 g, 20.9 mmol) in dichloromethane (100 mL) was added 4-(dimethylamino)pyridine (3.85 g, 31.5 mmol). The solution was cooled to 0 °C and a solution of *N*,*N*'-dicyclohexylcarbodiimide (4.74 g, 23.0 mmol) in dichloromethane (50 mL) was added dropwise over 1 hour. After warming to room temperature the reaction mixture was left to stir for 20 hours. The reaction mixture was filtrated and the filtrate washed with 5% $KHSO_4$ (3 x 100 mL) and saturated brine (1 x 100 mL). The organic phase was extracted and dried over $MgSO_4$ at 0 °C for 5 hours. The solution was filtered, glacial acetic acid (13.3 mL, 220 mmol) was added to the filtrate and the solution was cooled to 0 °C. Sodium borohydride (1.85 g, 50 mmol) was added portion wise over 1 hour before the reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was washed with water (2 x 100 mL) and saturated brine (100 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The mixture was purified by flash column chromatography to a give the desired compound.

5.13.1: (*S*)-*tert*-butyl 2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl)pyrrolidine-1-carboxylate 367o



N-Boc-L-proline (4.31 g, 20.0 mmol) was reacted under the standard protocol. The reaction mixture was purified by flash column chromatography (4:1 petrol:ethyl acetate) to a give the desired compound as a white solid (5.10 g, 78%); R_f (4:1 petrol:ethyl acetate) 0.32; mp 122-123 ^{o}C; $[\alpha]_D^{24}$ -22.6 (c 0.40, $CHCl_3$); IR (KBr, cm^{-1}) ν 2976, 2915 (C-H), 1784, 1749, 1675 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (1H, d, J = 4.5 Hz, NC*H*), 4.32 (1H, t, J = 7.9 Hz, C*H malonate*), 3.33 (2H, m, NCH_2), 2.32-2.23 (1H, CHCH_2CH), 2.12-1.87 (4H, m), 1.83 (3H, s, C(CH_3)$_2$), 1.74 (3H, s, C(CH_3)$_2$), 1.72-1.62 (1H, m), 1.41 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.5, 157.0, 105.3, 79.9, 55.8, 47.0, 45.6, 32.1, 32.0, 29.1, 28.8, 26.0, 24.0; HRMS (ESI) calcd for $C_{16}H_{24}NO_6$ $[M-H]^-$: m/z 326.1604, found 326.1590.

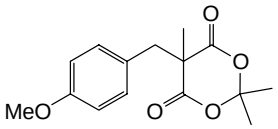
5.13.2: (*R*)-*tert*-butyl 1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-phenylpropan-2-ylcarbamate 367p



N-Boc-L-phenylalanine (5.32 g, 20.0 mmol) was reacted under the standard protocol. The reaction mixture was purified by flash column cohromatography (2:1 petrol:ethyl acetate) to a give the desired compound as a white solid (6.75 g, 90%); R_f (2:1 petrol:ethyl acetate) 0.24; $[\alpha]_D^{24}$ +4.6 (c = 1.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.17 (5H, m, Ar*H*), 4.57-4.42 (1H, m, C*H* Meldrum's acid), 4.37-4.09 (1H, m, NHC*H*), 3.91 (1H, brs, N*H*), 3.00-2.74 (2H, m, ArCH_2), 2.38-2.03 (2H, m, CHCH_2), 1.78 (3H, s, C(CH_3)$_2$), 1.74 (3H, s, C(CH_3)$_2$), 1.36 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.7, 165.6, 156.5, 137.2, 129.3, 128.6, 126.7, 105.1, 79.6, 50.0, 44.2, 41.8, 31.4, 28.5, 28.2, 26.0. Data identical to literature values.[15]

5.14 Alkylation of 5-Monoalkyl Meldrum's Acid Derivatives

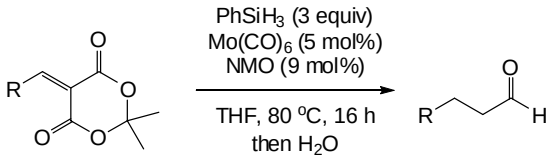
5.14.1: 5-(4-methoxybenzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione 380



To a solution of 5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367a** (529 mg, 2 mmol) and potassium carbonate (304 mg, 2.2 mmol) in *N*,*N*'-dimethylformamide (5 mL) was added methyl iodide (125 μL, 2mmol). The reaction mixture was stirred at room temperate for 1 hour. The reaction mixture was dissolved in ethyl acetate (50 mL) and washed with water (3 x 50 mL) and saturated brine (50 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo* to give the desired compound as a colourless solid (545 mg, 98%); mp (ethyl acetate) 86-88 ^{o}C (lit = 84 ^{o}C)[16]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (2H, d, *J* = 9.0 Hz, Ar*H*), 6.78 (2H, d, *J* = 9.0 Hz, Ar*H*), 3.75 (3H, s, OCH_3), 3.26 (2H, s, ArCH_2), 1.72 (3H, s, C(CH_3)$_2$), 1.60 (3H, s, C(CH_3)$_2$), 0.97 (3H, s, CCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.4, 159.5, 131.6, 127.8, 114.5, 105.6, 55.62, 52.8, 44.6, 29.8, 28.8, 26.1; HRMS (ESI) calcd for $C_{15}H_{18}NaO_5$ $[M+Na]^+$: *m*/*z* 301.1052, found 301.1051. Data identical to literature values values.[16]

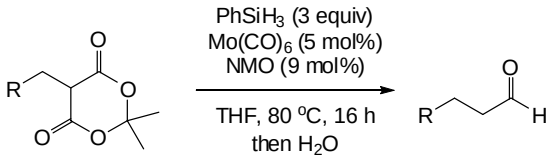
5.15 General Preparation of 3-Aryl Propionaldehydes

Method A



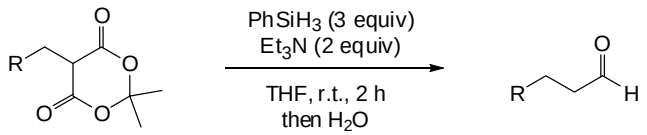
To a solution of alkylidene Meldrum's acid derivative (0.5 mmol), molybdenum hexacarbonyl (6.6 mg, 5 mol%) and *N*-methylmorpholine *N*-oxide monohydrate (5.9 mg, 9 mol%) in tetrahydrofuran (3.0 mL) was added phenylsilane (185 μL, 1.5 mmol). The resulting solution was stirred under an atmosphere of nitrogen at 80 ^{o}C for 16 h. After cooling to room temperature water (0.5 mL) was added and the solution stirred for 15 minutes. The solution was dissolved in ether (50 mL) was washed with 1 M NaOH (3 x 50 mL) followed by saturated brine (2 x 50 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The desired product was purified by flash column chromatography.

Method B



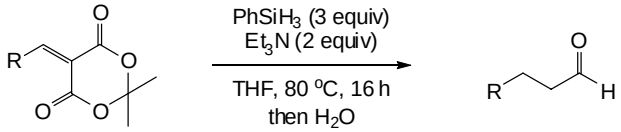
To a solution of 5-monoalkyl Meldrum's acid derivative (0.5 mmol), molybdenum hexacarbonyl (6.6 mg, 5 mol%) and *N*-methylmorpholine *N*-oxide monohydrate (5.9 mg, 9 mol%) in tetrahydrofuran (3.0 mL) was added phenylsilane (185 μL, 1.5 mmol). The resulting solution was stirred under an atmosphere of nitrogen at 80 ^{o}C for 16 h. After cooling to room temperature water (0.5 mL) was added and the solution stirred for 15 minutes. The solution was dissolved in ether (50 mL) was washed with 1 M NaOH (3 x 50 mL) followed by saturated brine (2 x 50 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The desired product was purified by flash column chromatography.

Method C



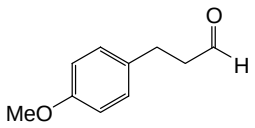
To a solution of 5-alkyl Meldrum's acid derivative (0.5 mmol) in tetrahydrofuran (3 mL) was added triethylamine (139 μL, 1.0 mmol) followed by phenylsilane (185 μL, 1.5 mmol). The resulting solution was stirred for 2 hours at room temperature. Water (0.5 mL) was added to the solution and stirred for 15 minutes. The reaction mixture was dissolved in diethyl ether (50 mL) and washed with water (2 x 50 mL) then with saturated brine (50 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo* and purified by column chromatography to give the desired product.

Method D



To a solution of alkylidene Meldrum's acid derivative (0.5 mmol) tetrahydrofuran (3.0 mL) was added triethylamine (139μL, 1.0 mmol) and phenylsilane (185 μL, 1.5 mmol). The resulting solution was stirred at 80 ^{o}C for 16 h. After cooling to room temperature water (0.5 mL) was added and the solution stirred for 15 minutes. The solution was dissolved in ether (25 mL) was washed with water (2 x 25 mL) followed by saturated brine (25 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The desired product was purified by flash column chromatography.

5.15.1: 3-(4-methoxyphenyl)-propanal 368a



5-(4-methoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **328a** (131 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (petrol:ethyl acetate 11:1), as a colourless oil (70.1 mg, 85%).

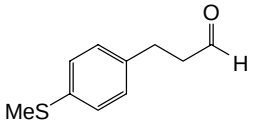
5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367a** (132 mg, 0.5 mmol) was reacted using method B to give the desired product, purified by flash column chromatography, as a colourless oil (59.4 mg, 72%).

5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367a** (132 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography, as a colourless oil (68.9 mg, 84%).

5-(4-methoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **328a** (131 mg, 0.5 mmol) was reacted using method D to give the desired product, purified by flash column chromatography, as a colourless oil (29.4 mg, 36%).

R_f (11:1 petrol:ethyl acetate) 0.21; IR (neat, cm^{-1}) *v* 2840, 2730 (C-H), 1716 (C=O), 1246 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (1H, t, *J* = 1.5 Hz, C*H*O), 7.11 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.84 (2H, d, *J* = 8.7 Hz, Ar*H*), 3.78 (3H, s, CH_3), 2.91 (2H, t, *J* = 7.2 Hz, ArCH_2), 2.77-2.72 (2H, m, CH_2CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.3, 158.5, 132.7, 129.7, 114.4, 55.7, 46.0, 27.7; HRMS (ESI) calcd for $C_{10}H_{12}NaO_2$ $[M+Na]^+$: *m/z* 187.0735, found 187.0738. Data identical to literature values.[17]

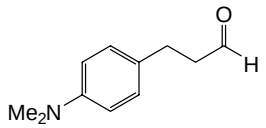
5.15.2: 3-(4-thiomethylbenzene)-propanal 368b



5-(4-thiomethylbenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **328b** (139 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (11:1 petrol:ethyl acetate), as a colourless oil (44 mg, 66%); R_f (11:1 petrol:ethyl acetate) 0.24; IR (neat, cm^{-1}) *v* 2824, 2727 (C-H); 1722 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (1H, t, *J* = 1.5 Hz, C*H*O), 7.20 (2H, d, *J* = 8.7 Hz, Ar), 7.12 (2H, d, *J* = 8.7 Hz, Ar), 2.92 (2H, t, *J* = 7.2 Hz, ArCH_2), 2.79-2.73 (2H, m, CH_2CHO); ^{13}C NMR

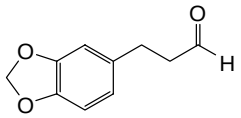
(75.5 MHz, $CDCl_3$) δ 201.9, 137.7, 136.5, 129.3, 127.5, 45.7, 31.4, 28.0, 16.6, HRMS (EI) calcd for $C_{10}H_{16}NOS$ $[M+NH_4]^+$: *m/z* 198.0947, found 198.948; Anal. calcd for $C_{10}H_{12}OS$: C 66.6, H 6.71, found: C 66.3, H 6.88.

5.15.3: 3-(4-dimethylaminobenzene)-propanal 368c



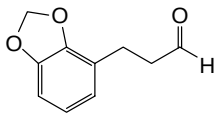
5-(4-dimethylaminobenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **328c** (126 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (10:1 petrol:ethyl acetate), as a colourless oil (71.8 mg, 81%); R_f (10:1 petrol:ethyl acetate) 0.19; IR (neat, cm^{-1}) *v* 2826, 2729 (C-H); 1722 (C=O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.82 (1H, t, *J* = 1.5 Hz, C*H*O), 7.07 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.70 (2H, d, *J* = 8.7 Hz, Ar*H*), 2.92 (6H, s, N(CH_3)$_2$), 2.89 (2H, t, *J* = 7.2 Hz, ArCH_2), 2.76-2.70 (2H, m, CH_2CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.7, 149.7, 129.3, 128.6, 113.4, 46.1, 41.2, 27.6; HRMS (EI) calcd for $C_{11}H_{16}NO$ $[M+H]^+$: *m/z* 178.1232, found 178.1228.

5.15.4: 3-(benzo[1,3]dioxol-5-yl)propanal 368d



5-(benzo[1,3]dioxol-5-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **328d** (138.1 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by column chromatography (petrol : ethyl acetate 6:1), as a colourless oil (58.3 mg, 65%); R_f (6:1 petrol:ethyl acetate) 0.29; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (1H, t, *J* = 1.5 Hz, C*H*O), 6.72 (1H, d, *J* = 7.8 Hz, Ar*H*), 6.68-6.62 (2H, m, Ar*H*), 5.91 (2H, s, OCH_2O), 2.87 (2H, t, *J* = 7.3 Hz, ArCH_2), 2.74-2.70 (2H, m, CH_2CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.2, 148.1, 146.4, 134.5, 121.5, 109.2, 108.7, 101.3, 46.0, 28.3; HRMS (EI) calcd for $C_{10}H_{10}NaO_3$ $[M+Na]^+$: *m/z* 201.0528, found 201.0532. Data identical to literature values.[18]

5.15.5: 3-(benzo[1,3]-dioxol-4-yl)-propanal 368e

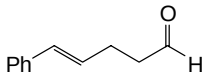


5-(benzo[*d*][1,3]dioxol-4-ylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **328e** (138 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (petrol : ethyl acetate 11:1), as a colourless oil (69.4 mg, 78%).

5-(benzo[*d*][1,3]dioxol-4-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **367e** (139 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography, as a colourless oil (69.2 mg, 78%).

R_f (11:1 petrol:ethyl acetate) 0.24; IR (neat, cm^{-1}) *v* 2828, 2729 (C-H); 1724 (C=O); 1252 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (1H, t, *J* = 1.3 Hz, C*H*O), 6.79-6.65 (3H, m, Ar*H*), 5.93 (2H, s, -OCH_2O-), 2.92 (2H, t, *J* = 7.3 Hz, ArCH_2), 2.82-2.75 (2H, m, CH_2CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.0, 147.6, 145.8, 128.2, 122.8, 122.1, 107.4, 101.0, 43.7, 22.7; HRMS (ESI) calcd for $C_{10}H_{10}NaO_3$ $[M+Na]^+$: *m*/*z* 201.0528, found 201.0524.

5.15.6: (*E*)-5-phenylpent-4-enal 367f

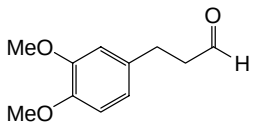


2,2-dimethyl-5-(3-phenyl-allylidene)-[1,3]dioxane-4,6-dione **328f** (129 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (12:1 petrol:ethyl acetate), as a colourless oil (31.2 mg, 39%).

5-cinnamyl-2,2-dimethyl-[1,3]dioxane-4,6-dione **367f** (130 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography (petrol : ethyl acetate 12:1), as a colourless oil (64.2 mg, 80%).

R_f (12:1 petrol:ethyl acetate) 0.26; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (1H, t, *J* = 1.3 Hz, C*H*O), 7.36-7.28 (4H, m, Ar*H*), 7.24-7.19 (1H, m, Ar*H*), 6.4 (1H, dt, J^1 = 15.8 Hz, J^2 = 1.3 Hz, PhC*H*), 6.21 (1H, dt, J^1 = 15.8 Hz, J^2 = 6.4 Hz, PhCHC*H*), 2.66-2.61 (2H, m, CHCHCH_2), 2.59-2.51 (2H, m, CH_2CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.2, 137.6, 131.5, 129.0, 128.6, 127.7, 126.5, 43.7, 25.9; HRMS (ESI) calcd for $C_{11}H_{12}NaO$ $[M+Na]^+$: *m*/*z* 183.0786, found 183.0790. Data identical to literature values.[19]

5.15.7: 3-(3,4-dimethoxyphenyl)-propanal 368g

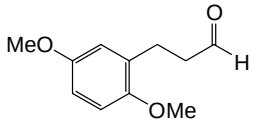


5-(3,4-dimethoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **328g** (146 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (4:1 petrol:ethyl acetate), as a colourless oil (51.2 mg, 53%).

5-(3,4-dimethoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367g** (147 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography, as a colourless oil (59.5 mg, 61%).

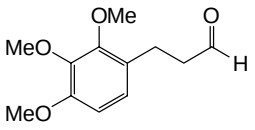
R_f (4:1 petrol:ethyl acetate) 0.30; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (1H, t, *J* = 1.5 Hz, C*H*O), 6.80 (1H, d, *J* = 8.5 Hz, Ar*H*), 6.74-6.71 (2H, m, Ar*H*), 3.87 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 2.90 (2H, t, *J* = 7.2 Hz, ArCH_2), 2.78-2.71 (2H, m, CH_2CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.1, 149.4, 147.9, 133.3, 120.5, 112.1, 111.8, 56.3, 56.2, 45.9, 28.2; HRMS (EI) calcd for $C_{11}H_{14}NaO_3$ $[M+Na]^+$: *m*/*z* 217.0841, found 217.0840. Data identical to literature values.[20]

5.15.8: 3-(2,5-dimethoxyphenyl)-propanal 368h



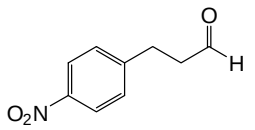
5-(2,5-dimethoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione **328h** (146 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (11:1 petrol:ethyl acetate), as a colourless oil (73.4 mg, 76%); R_f (11:1 petrol:ethyl acetate) 0.20; IR (neat, cm^{-1}) *v* 2836, 2729 (C-H); 1723 (C=O); 1225 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (1H, t, *J* = 1.5 Hz, C*H*O), 6.78-6.69 (3H, m, Ar*H*), 3.77 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 2.92 (2H, t, *J* = 7.2 Hz, ArCH_2), 2.74-2.68 (2H, m, CH_2CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.7, 153.9, 152.0, 130.2, 116.8, 111.9, 111.5, 56.1, 56.1, 44.3, 24.1; HRMS (EI) calcd for $C_{11}H_{15}O_3$ $[M+H]^+$: *m*/*z* 195.1021, found 195.1021.

5.15.9: 3-(2,3,4-trimethoxyphenyl)-propanal 367i



5-(2,3,4-trimethoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione **328i** (161 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by column chromatography (11:1 petrol:ethyl acetate), as a colourless oil (53.3 mg, 48%); R_f (11:1 petrol:ethyl acetate 0.26); IR (neat, cm^{-1}) ν 2826, 2728 (C-H); 1723 (C=O); 1248, 1232 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (1H, t, J = 1.5 Hz, C*H*O), 6.80 (1H, d, J = 8.7 Hz, Ar*H*), 6.57 (1H, d, J = 8.7 Hz, Ar*H*), 3.87 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 2.86 (2H, t, J = 7.5 Hz, ArCH_2), 2.72-2.66 (2H, m, CH_2CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.7, 152.9, 152.2, 142.6, 126.6, 124.2, 107.5, 61.2, 61.1, 56.4, 45.1, 23.2; HRMS (EI) calcd for $C_{12}H_{16}NaO_4$ $[M+Na]^+$: m/z 247.0946, found 247.0937.

5.15.10: 3-(4-nitrophenyl)-propanal 368j



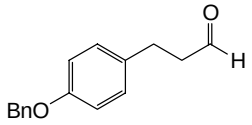
5-(4-nitrobenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **328j** (139 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (6:1 petrol:ethyl acetate), as a colourless crystalline solid (32.8 mg, 37%).

5-(4-nitrobenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367j** (140 mg, 0.5 mmol) was reacted using method B to give the desired product, purified by flash column chromatography, as a colourless crystalline solid (81.6 mg, 91%).

5-(4-nitrobenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367j** (140 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography, as a colourless crystalline solid (82.2 mg, 92%).

R_f (6:1 petrol:ethyl acetate) 0.19; mp (EtOH) 106-108 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (1H, t, J = 1.1 Hz, C*H*O), 8.14 (2H, d, J = 8.7 Hz, Ar*H*), 7.36 (2H, d, J = 8.7 Hz, Ar*H*), 3.05 (2H, t, 7.2 Hz, ArCH_2), 2.88-2.83 (2H, m, CH_2CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 200.6, 148.7, 147.0, 129.7, 124.2, 44.9, 28.2; HRMS (ESI) calcd for $C_9H_{10}NO_3$ $[M+H]^+$: m/z 180.0661, found 180.0660; Anal. calcd for $C_9H_9NO_3$: C 60.3, H 5.06, N 7.82, found: C 60.0, H 5.25, N 7.69. Data identical to literature values.[21]

5.15.11: 3-(4-benzyloxyphenyl)-propanal 368k

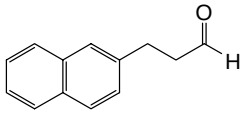


5-(4-benzyloxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **328k** (169 mg, 0.5 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (9:1 petrol:ethyl acetate), as a white solid (54.4 mg, 45%).

5-(4-benzyloxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367k** (170 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography, as a white solid (88.5 mg, 74% yield).

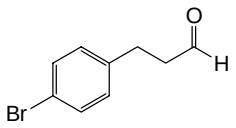
R_f (9:1 petrol:ethyl acetate) 0.27; mp (petrol) 87-88 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (1H, t, *J* = 1.5 Hz, C*H*O), 7.45-7.29 (5H, m, Ar*H*), 7.11 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.91 (2H, d, *J* = 8.7 Hz, Ar*H*), 5.05 (2H, s, PhCH_2O), 2.91 (2H, t, *J* = 7.5 Hz, ArCH_2), 2.75 (2H, m, CH_2CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.1, 157.7, 137.5, 133.0, 129.7, 129.0, 128.3, 127.9, 115.4, 70.5, 45.9, 27.7; HRMS (ESI) calcd for $C_{16}H_{16}NaO_2$ $[M+Na]^+$: *m*/*z* 263.1048, found *m*/*z* 263.1041; Anal. calcd for $C_{16}H_{16}O_2$: C 80.0, H 6.71, found: C 80.8, H 6.66. Data identical to literature values.[22]

5.15.12: 3-(2-naphthyl)-propanal 368l



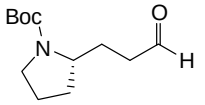
5-(2-nathphalen-2-methyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367l** (139 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography (12:1 petrol:ethyl acetate), as a yellow oil (58.5 mg, 65%); R_f (12:1 petrol:ethyl acetate) 0.24; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.85 (1H, t, *J* = 1.4 Hz, C*H*O), 7.85-7.77 (3H, m, Ar*H*), 7.65 (1H, s, Ar*H*), 7.53-7.42 (2H, m, Ar*H*), 7.34 (1H, dd, J^1 = 8.5 Hz, J^2 = 1.9 Hz, Ar*H*), 3.13 (2H, d, *J* = 7.6 Hz, ArCH_2), 2.90-2.83 (2H, m, CH_2CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.9, 138.3, 134.0, 132.6, 128.7, 128.1, 127.9, 127.3, 126.9, 126.6, 125.9, 45.6, 28.7; HRMS (ESI) calcd for $C_{13}H_{11}O$ $[M-H]^-$: *m*/*z* 183.0810, found 183.0810. Data identical to literature values.[23]

5.15.13: 3-(4-bromophenyl)-propanal 368n



5-(4-bromobenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367n** (157 mg, 0.5 mmol) was reacted using method C to give the desired product, purified by flash column chromatography (12:1 petrol:ethyl acetate), as a colourless oil (84.3 mg, 79%); R_f (12:1 petrol:ethyl acetate) 0.28; IR (neat, cm^{-1}) 2826, 2728 (CHO); 1723 (C=O); 650 (C-Br); ^1H NMR (250 MHz, $CDCl_3$) δ 9.80 (1H, t, *J* = 1.3 Hz, C*H*O), 7.39 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.07 (2H, d, *J* = 8.5 Hz, Ar*H*), 2.91 (2H, t, *J* = 7.3 Hz, ArCH_2), 2.77 (2H, m, CH_2CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 199.9, 138.3, 130.6, 129.0, 119.0, 44.0, 26.4; HRMS (ESI) calcd for C_9H_9BrNaO $[M+Na]^+$: *m*/*z* 234.9729, found 234.9735.

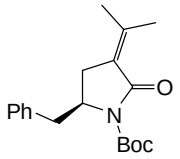
5.15.14: (*S*)-*tert*-butyl 2-(3-oxopropyl)pyrrolidine-1-carboxylate 368o



To a solution of (*S*)-*tert*-butyl 2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl)pyrrolidine-1-carboxylate **367o** (818.4 mg, 2.5 mmol) in tetrahydrofuran (15 mL) was added triethylamine (700 μL, 5 mmol) followed by phenylsilane (925 μL, 7.5 mmol). The solution was allowed to stir for 2 hours at room temperature before water (5 mL) was added. The reaction mixture was dissolved in diethyl ether (100 mL) and washed with water (2 x 100 mL) followed by saturated brine (100 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (10:1 petrol:ethyl acetate) to give the desired product, a mixture of rotamers, as a colourless oil (428 mg, 75%); R_f(10:1 petrol:ethyl acetate) 0.21; $[\alpha]_D^{24}$ +160.3 (c 0.56, $CHCl_3$); IR (neat, cm^{-1}) *ν* 2880, 2722 (C-H), 1724, 1690 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (1H, brs, C*H*O), 3.80 (1H, brs, BocNCH_2), 3.38-3.20 (2H, m, BocNCH_2 and BocNC*H*), 2.53-2.37 (2H, m, CH_2CHO), 2.00-1.55 (6H, m), 1.41 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.6 and 202.2, 155.25, 79.8 and 79.5, 56.8, 46.9 and 46.6, 41.2, 31.2 and 30.6, 28.9, 27.4, 24.1 and 23.3; HRMS (ESI) calcd for $C_{12}H_{21}NNaO_3$ $[M+Na]^+$: *m*/*z* 250.1419, found : *m*/*z* 250.1417.

5.16 Synthesis of 3,5-Disubstituted Pyrrolidines

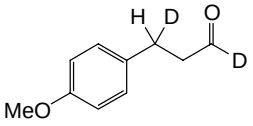
5.16.1: (*S*)-*tert*-butyl 5-benzyl-2-oxo-3-(propan-2-ylidene)pyrrolidine-1-carboxylate 410



To a solution of (*R*)-*tert*-butyl 1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-phenylpropan-2-ylcarbamate **367p** (189 mg, 0.5 mmol) in tetrahydrofuran (3 mL) was added triethylamine (139 μL, 1.0 mmol) followed by phenylsilane (185 μL, 1.5 mmol). The reaction mixture allowed to stir at ambient temperature for 20 hours. The reaction mixture was dissolved in ethyl acetate (50 mL) and washed with water (2 x 50 mL) and saturated brine (50 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (12:1 petrol:ethyl acetate) to give the desired compound as a colourless oil (71.4 mg, 45%); R_f (12:1 petrol:ethyl acetate) 0.20; IR (neat, cm^{-1}) ν 2979, 2932 (C-H), 1772, 1707 (C=O), 1662 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.17 (5H, m, Ar*H*), 4.34-4.26 (1H, m, NC*H*), 3.18 (1H, dd, J^1 = 13.2 Hz, J^2 = 3.4 Hz, ArCH_2), 2.53 (1H, dd, J^1 = 13.2 Hz, J^2 = 9.4 Hz, ArCH_2), 2.47-2.37 (2H, m, CCH_2CH), 2.21 (3H, s, C(CH_3)$_2$), 1.75 (3H, s, C(CH_3)$_2$), 1.59 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.3, 151.3, 149.2, 137.7, 129.8, 129.0, 127.1, 123.4, 82.9, 55.4, 41.3, 29.0, 28.6, 24.5, 20.3; HRMS (ESI) calcd for $C_{19}H_{25}NNaO_3$ $[M+Na]^+$: *m*/*z* 338.1732, found 338.1715.

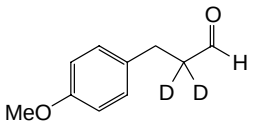
5.17 Deuterium Labelling Studies

5.17.1: 1,3-dideuterated-3-(4-methoxyphenyl) propionaldehyde 382a



To a solution of 5-(4-methoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **328a** (131 mg, 0.5 mmol), molybdenum hexacarbonyl (6.6 mg, 5 mol%) and *N*-methylmorpholine *N*-oxide (5.9 mg, 0.044 mmol, 9mol%) in tetrahydrofuran (3 mL) was added trideuteriophenylsilane (185 μL, 1.5 mmol). The resulting solution was stirred under an atmosphere of nitrogen at 80 ^{o}C for 16 h. After cooling to room temperature water (0.5 mL) was added and the solution stirred for 15 minutes. The solution was dissolved in ether (50 mL) was washed with 1 M NaOH (3 x 50 mL) followed by brine (2 x 50 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The desired product was isolated by flash column chromatography (11:1 petrol:ethyl acetate) as a colourless oil (65.1 mg, 79%); 100% deuterium incorportation; R_f (11:1 petrol:ethyl acetate) 0.21; IR (neat, cm^{-1}) *v* 2081 (C-D), 1709 (C=O), 1246 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.84 (2H, d, *J* = 8.7 Hz, Ar*H*), 3.79 (3H, s, OCH_3), 2.92-2.86 (1H, m, C*H*D), 2.74 (2H, d, *J* = 7.9 Hz, CH_2CDO); ^{2}H NMR (77 MHz, DCM) δ 9.75 (s, C*D*O), 2.84 (s, ArCH*D*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.9 (t, *J* = 26.0 Hz), 158.5, 132.7, 129.6, 114.4, 55.7, 45.7, 29.3 (t, *J* = 19.6 Hz); HRMS (EI) calcd for $C_{10}H_{14}D_2NO$ [M+NH_4^+]: *m*/*z* 189.0855, found: *m*/*z* 189.0855.

5.17.2: Preparation of α,α-dideuterated-3-(4-methoxyphenyl) propionaldehyde 383a

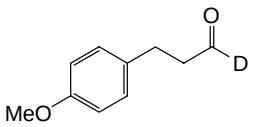


Procedure A : To a solution of 5-(4-methoxybenzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **328a** (131 mg, 0.5 mmol), molybdenum hexacarbonyl (6.6 mg, 5 mol%) and *N*-methylmorpholine *N*-oxide monohydrate (5.9 mg, 0.044 mmol, 9mol%) in tetrahydrofuran (3 mL) was added phenylsilane (185 μL, 1.5 mmol). The resulting solution was stirred under an atmosphere of nitrogen at 80 ^{o}C for 16 h. After cooling to room temperature deuterium oxide (0.5 mL) was added and the solution stirred for 15 minutes.

Procedure B : To a solution of 5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367a** (132 mg, 0.5 mmol) in tetrahydrofuran (3 mL) was added triethylamine (139 μL, 1.0 mmol) and phenylsilane (183 μL, 1.5 mmol). The reaction mixture was allowed to stir for 2h at room temperature under an atmosphere of nitrogen. Deuterium oxide (1.0 mL) was added to the reaction mixture and stirred for 15 minute.

Work-up : The reaction mixture was dissolved in diethyl ether (50 mL) and washed with water (50 mL) and brine (50 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The desired product was isolated by flash column chromatography (11:1 petrol:ethyl acetate) as a colourless oil (Procedure A : 61.5 mg, 75%; Procedure B : 68.0 mg, 82% yield); 73% deuterium incorporation;R_f (11:1 petrol:ethyl acetate) 0.21; IR (neat, cm^{-1}) *v* 2836, 2725 (C-H), 1723 (C=O), 1249 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (1H, s, C*H*O), 7.11 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.84 (2H, d, *J* = 8.7 Hz, Ar*H*), 3.78 (3H, s, OCH_3), 2.89 (2H, s, ArCH_2); ^{2}H NMR (77 MHz, DCM) δ 2.64 (s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.3, 158.5, 132.7, 129.6, 114.4, 55.7, 45.5 (t, *J* = 28.5 Hz CD_2), 27.6; HRMS (EI) calcd for $C_{10}H_{10}D_2NaO$ $[M+Na]^+$: *m*/*z* 189.0855, found: *m*/*z* 189.0858.

5.17.3: Preparation of 1-deuterated-3-(4-methoxyphenyl) propionaldehyde 412a

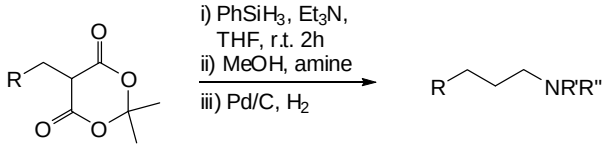


To a solution of 5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **467a** (132 mg, 0.5 mmol) in tetrahydrofuran (3 mL) was added triethylamine (139 μL, 1.0 mmol) and trideuterophenylsilane[24] (190 μL, 1.5 mmol). The reaction mixture was allowed to stir for 2h at room temperature under an atmosphere of nitrogen. Water (1.0 mL) was added to the reaction mixture and stirred for 15 minute. The reaction mixture was dissolved in diethyl ether (50 mL) and washed with water (50 mL) and brine (50 mL). The organic phase was extracted, dried over $MgSO_4$ and concentrated *in vacuo*. The desired product was isolated by flash column chromatography (11:1 petrol:ethyl acetate) as a colourless oil (70.4 mg, 85%); 100% deuterium incorporation; R_f (11:1 petrol:ethyl acetate) 0.21; IR (neat, cm^{-1}) *v* 2279 (C-D), 1712 (C=O), 1247 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.84 (2H, d, *J* = 8.7 Hz, Ar*H*), 3.78 (3H, s, OCH_3), 2.91 (2H, t, *J* = 7.5 Hz, ArCH_2) 2.74 (2H, t, *J* = 7.5 Hz, CH_2CDO); ^{2}H NMR (77 MHz, DCM) δ 9.75 (s); ^{13}C NMR

(75.5 MHz, $CDCl_3$) δ 201.9 (t, *J* = 26.0 Hz), 158.5, 132.8, 129.6, 114.4, 55.7, 45.8, 27.7; HRMS (EI) calcd for $C_{10}H_{10}DNaO$ $[M+Na]^+$: *m*/*z* 187.0855, found: *m*/*z* 187.0854.

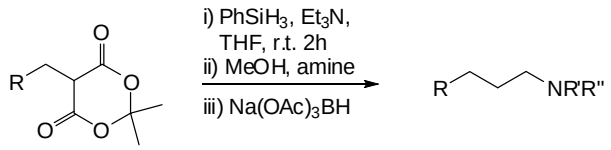
5.18 One-Pot Aldehyde Formation Reductive Amination

Method A: Using Pd/C, H_2



To a solution of 5-monoalkyl Meldrum's acid (0.5 mmol) in tetrahydrofuran (3 mL) was added triethylamine (139 μL, 1 mmol) followed by phenylsilane (185 μL, 1.5 mmol). The reaction mixture was stirred for 2 hours at room temperature. Methanol (1 mL) was added to the reaction mixture and stirred for 15 minutes before amine was added (1 mmol) and stirred for a further hour. 10% palladium on activated carbon (50 mg) was added and hydrogen gas bubbled through the solution. The reaction mixture was left for 16 hours. The reaction mixture was then passed through a pad of celite and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (25 mL) and washed with 1M $HCl_{(aq)}$ (3 x 25 mL). The aqueous phase was basified with 1M $NaOH_{(aq)}$ and washed with DCM (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*.

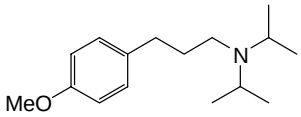
Method B: Using $Na(OAc)_3BH$



To a solution of 5-substituted Meldrum's acid derivative (0.5 mmol) in tetrahydrofuran (3 mL) was added triethylamine (139 μL, 1.0 mmol) followed by phenylsilane (185 μL, 1.5 mmol). The reaction mixture was stirred for 2 hours at room temperature. Methanol (1 mL) was added to the reaction mixture and stirred for 15 minutes before amine was added (1 mmol) and stirred for a further hour. Sodium triacetoxyborohydride (212 mg, 1.0 mmol) was added and the reaction mixture was left to stir for 16 hours. The reaction mixture was dissolved in ethyl acetate (25 mL) and the organic phase was then extracted with 1M $HCl_{(aq)}$ (3 x 25 mL). The combined aqueous phases basified with 1M $NaOH_{(aq)}$ and extracted with

DCM (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*.

5.18.1: *N,N*-diisopropyl-3-(4-methoxybenzene)propan-1-amine 414aa

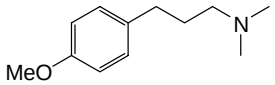


5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367a** (132 mg, 0.5 mmol) and diispropylamine **415a** (140 μL, 1.0 mmol) were reacted using method A to give the desired product as a colourless oil (77.7 mg, 63%).

5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367a** (132 mg, 0.5 mmol) and diispropylamine **415a** (140 μL, 1.0 mmol) were reacted using method B to give the desired product as a colourless oil (38.8 mg, 31%).

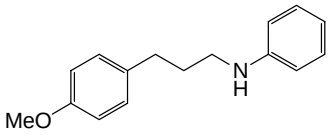
IR (neat, cm^{-1}) *v* 3001, 2968, 2875 (C-H), 1245 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.83 (2H, d, *J* = 8.7 Hz, Ar*H*), 3.79 (3H, s, OCH_3), 3.04 (2H, sept, *J* = 6.4 Hz, C*H*(CH_3)$_2$), 2.55 (2H, t, *J* = 7.5 Hz, ArCH_2), 2.45 (2H, t, *J* = 7.5 Hz, CH_2N), 1.74 (2H, quin, *J* = 7.5 Hz, $CH_2CH_2CH_2$), 1.01 (12H, d, *J* = 6.4 Hz, CH(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.5, 133.6, 128.2, 112.6, 54.2, 47.7, 44.0, 31.9, 31.7, 19.5; HRMS (ESI) calcd for $C_{16}H_{28}NO$ $[M+H]^+$: *m/z* 250.2171, found 250.2177.

5.18.2: *N,N*-dimethyl-3-(4-methoxybenzene))propan-1-amine 414ab



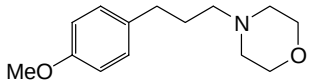
5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367a** (132 mg, 0.5 mmol) and dimethylamine (2M solution in THF) **415b** (1 mL, 1.0 mmol) were reacted using method A to give the desired product, purified by flash column chromatography (98:2 ethyl acetate:methanol), as a colourless oil (50.0 mg, 52%); R_f (98:2 ethyl acetate:methanol) 0.18; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.82 (2H, d, *J* = 8.7 Hz, Ar*H*), 3.78 (3H, s, OCH_3), 2.58 (2H, t, *J* = 7.5 Hz, ArCH_2), 2.28 (2H, t, *J* = 7.5 Hz, NCH_2), 2.22 (6H, s, N(CH_3)$_2$), 1.76 (2H, quin, *J* = 7.5 Hz, $CH_2CH_2CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.1, 134.7, 129.6, 114.1, 59.7, 55.6, 45.9, 33.1, 30.1; HRMS (ESI) calcd for $C_{12}H_{20}NO$ $[M+H]^+$: *m/z* 194.1545, found 194.1540. Data identical to literature values.[25]

5.18.3: *N*-phenyl-3-(4-methoxybenzene)propane-1-amine 414ac



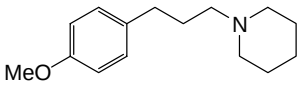
5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367a** (132 mg, 0.5 mmol) and aniline **415c** (91 μL, 1.0 mmol) were reacted using method A to give the desired product, purified by flash column chromatography (ethyl acetate), as a colourless oil (57.9 mg, 48%); R_f (ethyl acetate) 0.22; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (2H, dd, J^1 = 8.7 Hz, J^2 = 7.5 Hz, Ar*H*), 7.18 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.91 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.76 (1H, t, *J* = 7.5 Hz, Ar*H*), 6.64 (2H, d, *J* = 7.5 Hz, Ar*H*), 3.85 (3H, s, OCH_3), 3.32 (1H, brs, N*H*), 3.18 (2H, t, *J* = 7.2 Hz, ArCH_2), 2.74 (2H, t, *J* = 7.2 Hz, NCH_2), 1.97 (2H, quin, *J* = 7.2 Hz, $CH_2CH_2CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.8, 147.3, 132.7, 128.3, 128.2, 116.1, 112.8, 111.7, 54.2, 42.3, 31.4, 30.2; HRMS (ESI) calcd for $C_{16}H_{20}NO$ $[M+H]^+$: *m*/*z* 242.1545, found 242.1528. Data identical to literature values.[26]

5.18.4: 4-(3-(4-methoxyphenyl)propyl)morpholine 414ad



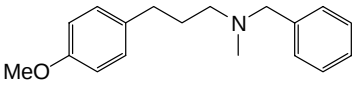
5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367a** (132 mg, 0.5 mmol) and morpholine **415d** (88 μL, 1.0 mmol) were reacted using method A to give the desired product, purified by flash column chromatography (ethyl acetate), as a colourless oil (48.0 mg, 41%); R_f (ethyl acetate) 0.23; IR (neat, cm^{-1}) *ν* 3011, 2944, 2859, 2813 (C-H), 1246, 1117 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.81 (2H, d, *J* = 8.7 Hz, Ar*H*), 3.77 (3H, s, OCH_3), 3.70 (4H, t, *J* = 4.5 Hz, O(CH_2)$_2$), 2.58 (2H, t, *J* = 7.5 Hz, ArCH_2), 2.42 (4H, t, *J* = 4.5 Hz, N(CH_2)$_2$), 2.34 (2H, t, *J* = 7.5 Hz, NCH_2) 1.77 (2H, quin, *J* = 7.5 Hz, $CH_2CH_2CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.2, 134.5, 129.7, 114.1, 67.4, 58.7, 55.6, 54.1, 33.1, 28.9; HRMS (ESI) calcd for $C_{14}H_{22}NO_2$ $[M+H]^+$: *m*/*z* 236.1651, found 236.1638.

5.18.5: 1-(3-(4-methoxyphenyl)propyl)piperidine 414ae



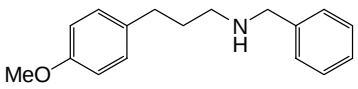
5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367a** (132 mg, 0.5 mmol) and piperidine **415e** (0.1 mL, 1.0 mmol) were reacted using method A to give the desired product, purified by flash column chromatography (ethyl acetate), as a colourless oil (57.9 mg, 50%); R_f (ethyl acetate) 0.24; IR (neat, cm^{-1}) *v* 2938, 2855, 2804, 2769 (C-H), 1245 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.81 (2H, d, *J* = 8.7 Hz, Ar*H*), 3.77 (3H, s, OCH_3), 2.56 (2H, t, *J* = 7.9 Hz, ArCH_2), 2.38-2.28 (6H, m, N(CH_2)$_3$) 1.79 (2H, quin, *J* = 7.9 Hz, $CH_2CH_2CH_2$), 1.58 (4H, quin, *J* = 5.7 Hz, CH_2), 1.46-1.38 (2H, m, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.1, 134.8, 129.6, 114.1, 59.3, 55.6, 55.0, 33.4, 29.3, 26.4, 24.9; HRMS (ESI) calcd for $C_{15}H_{24}NO$ $[M+H]^+$: *m*/*z* 234.1858, found 234.1857.

5.18.6: *N*-benzyl-*N*-methyl-3-(4-methoxybenzene)propane-1-amine 414af



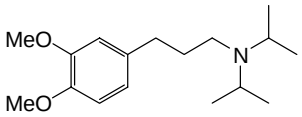
5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367a** (132 mg, 0.5 mmol) and *N*-benzyl-*N*-methylamine **415f** (0.1 mL, 1.0 mmol) were reacted using method A to give the desired product, purified by flash column chromatography (ethyl acetate), as a colourless oil (68.1 mg, 52%); R_f (ethyl acetate) 0.18; IR (neat, cm^{-1}) *v* 3028, 2939, 2836, 2790 (C-H), 1246 (C-O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36-7.27 (5H, m, Ar*H*), 7.10 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.83 (2H, d, *J* = 8.5 Hz, Ar*H*), 3.80 (3H, s, OCH_3), 3.52 (2H, s, NCH_2Ph), 2.60 (2H, t, *J* = 7.6 Hz, ArCH_2), 2.43 (2H, t, *J* = 7.6 Hz, CH_2N), 2.21 (3H, s, NCH_3), 1.83 (2H, quin, *J* = 7.9 Hz, $CH_2CH_2CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.1, 140.0, 134.9, 129.7, 129.5, 128.6, 127.3, 114.1, 62.7, 57.2, 55.7, 42.6, 33.1, 29.8; HRMS (EI) calcd for $C_{18}H_{24}NO$ $[M+H]^+$: *m*/*z* 270.1858, found 270.1853.

5.18.7: *N*-benzyl-3-(4-methoxybenzene)propane-1-amine 414ag



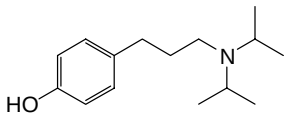
5-(4-methoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367a** (132 mg, 0.5 mmol) and benzylamine **415g** (0.11 mL, 1.0 mmol) were reacted using method A to give the desired product (47.8 mg, 37%); IR (neat, cm^{-1}) *v* 3064 (N-H), 3030, 3004, 2955, 2836 (C-H) 1249 (C-O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28-7.14 (5H, m, Ar*H*), 7.01 (2H, d, *J* = 8.8 Hz, Ar*H*), 6.74 (2H, d, *J* = 8.8 Hz, Ar*H*), 3.70 (5H, s, OCH_3 and NCH_2Ph), 2.58 (2H, t, *J* = 7.3 Hz, ArCH_2), 2.52 (2H, t, *J* = 7.3 Hz, CH_2N), 2.25 (1H, brs, N*H*), 1.72 (2H, quin, *J* = 7.3 Hz, $CH_2CH_2CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.7, 139.4, 133.2, 128.2, 127.4, 127.1, 125.9, 112.7, 54.2, 53.0, 47.9, 31.7, 30.9; HRMS (EI) calcd for $C_{17}H_{22}NO$ $[M+H]^+$: *m*/*z* 256.1701, found 256.1686.

5.18.8: *N,N*-diisopropyl-3-(3,4-dimethoxyphenyl)propan-1-amine 414ga



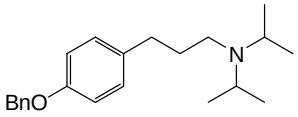
5-(3,4-dimethoxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367g** (147 mg, 0.5 mmol) and diisopropylamine **415a** (140 μL, 1.0 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (4:1 petrol:ethyl acetate), as a colourless oil (81.2 mg, 56%); R_f (4:1 petrol:ethyl acetate) 0.27; IR (neat, cm^{-1}) *v* 2963, 2902, 2877 (C-H), 1261, 1235 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80-6.70 (3H, m, Ar*H*), 3.87 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.03 (2H, sept, *J* = 6.4 Hz, NC*H*$(CH_3)_2$), 2.55 (2H, t, *J* = 7.9 Hz, ArCH_2), 2.44 (2H, t, *J* = 7.9 Hz, CH_2N), 1.74 (2H, quin, *J* = 7.5 Hz, $CH_2CH_2CH_2$), 1.00 (12H, d, *J* = 6.4 Hz, NCH(C$H_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.2, 147.4, 135.6, 120.5, 112.0, 111.5, 56.3, 56.2, 48.8, 45.5, 33.6, 21.0, 18.6; HRMS (ESI) calcd for $C_{17}H_{30}NO_2$ $[M+H]^+$: *m*/*z* 280.2277, found 280.2259.

5.18.9: *N,N*-diisopropyl-3-(4-hydroxyphenyl)propan-1-amine 416ka



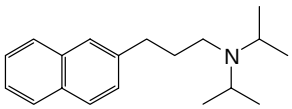
5-(4-benzyloxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367k** (170 mg, 0.5 mmol) and diisopropylamine **415a** (140 μL, 1.0 mmol) was reacted using method A to give the desired product as a colourless oil (67.3 mg, 57%); IR (neat, cm^{-1}) *v* 3414 (O-H), 2945, 2853 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.75 (2H, d, *J* = 8.7 Hz, Ar*H*), 3.09 (2H, sept, *J* = 6.4 Hz, NC*H*$(CH_3)_2$), 2.50 (2H, t, *J* = 7.5 Hz, ArCH_2), 2.47 (2H, t, *J* = 7.5 Hz, CH_2N), 1.77 (2H, quin, *J* = 7.5 Hz, $CH_2CH_2CH_2$), 1.04 (12H, d, *J* = 6.4 Hz, NCH(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.6, 134.2, 129.7, 116.2, 49.3, 45.6, 33.3, 33.0, 20.8; HRMS (ESI) calcd for $C_{15}H_{26}NO$ $[M+H]^+$: *m*/*z* 236.2014, found 236.2004.

5.18.10: *N,N*-diisopropyl-3-(4-benzyloxyphenyl)propan-1-amine 414ka



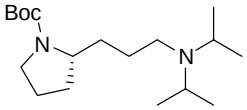
5-(4-benzyloxybenzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367k** (170 mg, 0.5 mmol) and diisopropylamine **415a** (140 μL, 1.0 mmol) was reacted using method B to give the desired product as a colourless oil (52.8 mg, 32%); IR (neat, cm^{-1}) *v* 2968, 2855 (C-H) 1238 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.30 (5H, m, Ar*H*), 7.12 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.91 (2H, d, *J* = 8.7 Hz, Ar*H*), 5.05 (2H, s, PhCH_2O), 3.05 (2H, sept, *J* = 6.4 Hz, NC*H*$(CH_3)_2$), 2.56 (2H, t, *J* = 7.9 Hz, ArC*H*$_2$), 2.46 (2H, t, *J* = 7.9 Hz, CH_2N), 1.76 (2H, quin, *J* = 7.9 Hz, $CH_2CH_2CH_2$), 1.03 (12H, d, *J* = 6.4 Hz, NCH(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.8, 136.2, 133.9, 128.2, 127.5, 126.8, 126.45, 113.6, 69.0, 49.0, 47.9, 44.0, 31.7, 19.5; HRMS (ESI) calcd for $C_{22}H_{32}NO$ $[M+H]^+$: *m*/*z* 326.2484, found 326.2483.

5.18.11: *N,N*-diisopropyl-3-(2-Naphthyl)propan-1-amine 414la



5-(2-nathphalen-2-methyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **367l** (139 mg, 0.5 mmol) and diisopropylamine **415a** (140 μL, 1.0 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (4:1 petrol:ethyl acetate), as a yellow oil (55.1 mg, 41%); R_f (4:1 petrol:ethyl acetate) 0.25; IR (neat, cm^{-1}) *v* 2978, 2912, 1845, (C-H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.65 (3H, m, Ar*H*), 7.65 (1H, s, Ar*H*), 7.50-7.40 (2H, m, Ar*H*), 7.37 (1H, dd, J^1 = 8.7 Hz, J^2 = 1.9 Hz, Ar*H*), 3.06 (2H, sept, *J* = 6.6 Hz, NC*H*$(CH_3)_2$), 2.80 (2H, t, *J* = 7.5 Hz, ArCH_2), 2.52 (2H, t, *J* = 7.5 Hz, CH_2N), 1.87 (2H, quin, *J* = 7.5 Hz, $CH_2CH_2CH_2$), 1.04 (12H, d, *J* = 6.6 Hz, NCH$(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 140.7, 134.1, 132.4, 128.2, 128.0, 127.8, 126.7, 126.4, 126.2, 125.4, 49.0, 45.4, 34.3, 33.1, 21.1; HRMS (ESI) calcd for $C_{19}H_{28}N$ $[M+H]^+$: *m*/*z* 270.2222, found : *m*/*z* 270.2204.

5.18.12: (*R*)-*tert*-butyl 2-(3-(diisopropylamino)propyl)pyrrolidine-1-carboxylate 414o



(*S*)-*tert*-butyl 2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl)pyrrolidine-1-carboxylate **367o** (164 mg, 0.5 mmol) and diisopropylamine **415a** (140 μL, 1.0 mmol) was reacted using method A to give the desired product, purified by flash column chromatography (ethyl acetate), as a colourless oil (95.1 mg, 61%); R_f (ethyl acetate) 0.28; $[\alpha]_D^{24}$ +383.3 (c 0.06, $CHCl_3$); IR (neat, cm^{-1}) 2971, 2875 (C-H), 1680 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (1H, brs, BocNCH_2), 3.40-3.25 (2H, m, BocNCH_2 and BocNC*H*), 2.99 (2H, sept, *J* = 6.4 Hz, NC*H*$(CH_3)_2$), 2.45 (2H, m NCH_2), 2.00-1.59 (5H, m), 1.46 (9H, s, C$(CH_3)_3$), 1.44-1.18 (3H, m), 1.00 (12H, d, *J* = 6.4 Hz, N(CH$(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.1, 79.3, 57.7, 48.9, 46.5, 45.8, 32.9, 31.1, 29.0, 24.2, 23.5, 21.1; HRMS (ESI) calcd for $C_{18}H_{37}N_2O_2$ $[M+H]^+$: *m*/*z* 313.2855, found : *m*/*z* 313.2844.

5.19 References

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